INVESTIGATING THE POTENTIAL OF RESPONDENT-DRIVEN SAMPLING TO REACH UNDIAGNOSED HIV-INFECTED PEOPLE WHO INJECT DRUGS

by
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Dissertation Abstract

Background Key populations such as people who inject drugs (PWID) lag behind in the UNAIDS 90-90-90 target, particularly at diagnosis. Respondent-driven sampling (RDS), a referral method that leverages peer network connections, is widely used in HIV surveillance and research for sampling hidden populations. The objective of this dissertation is to inform the utility and implementation of a strategy using RDS that seeks to improve levels diagnosis among HIV-infected PWID in India.

Methods First, we assessed the ability of RDS to reach undiagnosed HIV-infected PWID and other sub-populations compared to a venue-based strategy (integrated care centers [ICCs]). Next, we explored recruiter characteristics associated with recruiting undiagnosed HIV-infected PWID into an RDS sample and identified settings these characteristics predicted best. Lastly, we evaluated whether the efficiency of identification of undiagnosed HIV-infected PWID can be enhanced through alterations to the RDS coupon system.

Results RDS required screening fewer PWID and more rapidly identified undiagnosed HIV-infected PWID compared to ICCs. The number needed to recruit (NNR) - average number of PWID recruited/screened in order to find one undiagnosed HIV-infected PWID - for the ICC was 26 and for RDS was 11. HIV/HCV infection and factors associated with higher HIV risk were most strongly associated with recruiting an undiagnosed and viremic person who injects drugs living with HIV (PLWH). The prediction model performed best in areas with low harm reduction access and for recruiting an undiagnosed PLWH, prediction was best in settings with low

HIV/HCV services and high HIV incidence. The altered RDS coupon system in which individuals more likely to recruit undiagnosed HIV-infected PWID were provided more recruitment coupons did not significantly improve the efficiency of identification of undiagnosed PWID over the normal/traditional coupon system in which all participants receive the same number of coupons (NNR_{normal}=16.4 vs. $NNR_{altered}$=12.5; difference=3.9, 95% CI: -1.6 to 13.1).

Conclusion Reaching the UNAIDS 90-90-90 target requires using existing evidence-based prevention and care interventions but also finding new strategies to make marked progress in the care continuum. These findings highlight a potentially promising way to close the gap for PWID at diagnosis by utilizing RDS beyond its traditional sampling purpose.

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Chapter 1: Introduction

BACKGROUND

Global HIV epidemic

Since the peak of the HIV epidemic in the mid 1990's, there have been great strides made in slowing the global HIV epidemic. New infections have almost been halved and access to life-saving treatment has drastically improved, especially in the last decade, leading to decreased HIV/AIDS-related mortality. Despite these improvements, there were approximately 1.8 million people newly infected with HIV in 2017. In total, there are nearly 37 million people living with HIV and over 900,000 died of AIDS-related illnesses in 2017[1]. The largest burden of disease continues to be seen in eastern and southern Africa. However, this region also has some of the highest treatment coverage, resulting in recent sharp declines in new HIV infections among adults, compared to other regions such as Asia and the Pacific that have seen static trends in new infections and eastern Europe and central Asia where new infections increased 57% since 2010[2].

90-90-90 target

In 2014, UNAIDS set an ambitious target of 90-90-90 by 2020 to help end the global AIDS epidemic[3]. The goal is that 90% of those HIV-infected will be aware of their diagnosis; 90% of those diagnosed will be linked to clinical care and on sustained antiretroviral therapy (ART) and, ultimately, 90% of those on ART will achieve viral suppression. Fueled by the recognized individual and community benefits of expanded ART access and use, this new global approach promotes successful progression through all the steps of the HIV care continuum, which documents population levels of HIV diagnosis to viral suppression[4]. For individuals, initiation of and adherence to ART significantly slows clinical progression, reducing AIDS-associated

morbidity and mortality[5-7]. Additionally, early initiation of ART leads to reduced circulation of the virus which reduces the rate of transmission to sexual partners[8]. At a community-level, higher levels of ART coverage among populations has been shown to lead to decreased viral load in the community and a decrease in the number of new HIV infections[9,10]. The 90-90-90 target also prioritizes equity for all those affected by HIV, including key populations such as people who inject drugs (PWID), based on principles of human rights with continued efforts to eliminate stigma, discrimination, and social exclusion.

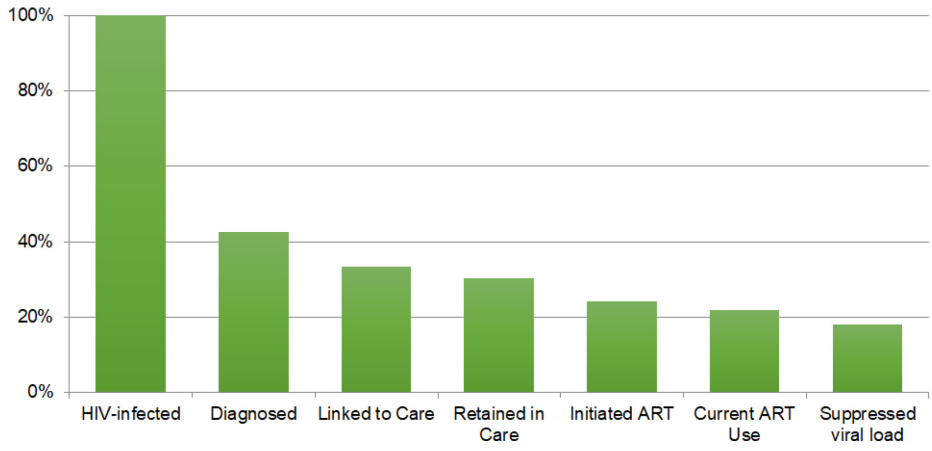
HIV epidemic in India

In 1986, Dr. Suniti Solomon along with her student, Sellappan Nirmala, were the first to find evidence of HIV in India after collecting samples from several female sex workers in Chennai, Tamil Nadu, in south India[11]. Like many other areas of the world, HIV continued to rise throughout the 1990's in India, with key populations - female sex workers, men who have sex with men (MSM), transgender individuals, and PWID being the hardest hit[12]. India continues to experience a concentrated HIV epidemic and has the third largest population of people living with HIV (PLHIV) and third largest number of AIDS deaths globally, only after South Africa and Nigeria[12].

Injection drug use is a major driver of established and new HIV epidemics in many low- and middle-income countries (LMICs)[13-15], including India, where there are an estimated 1.1 million PWID[16]. Transmission of HIV in injecting populations is largely due to sharing used injection paraphernalia (e.g., needles and syringes) with others, with a high estimated per-act probability of transmission[17]. Many PWID in India are impoverished and often experience social

marginalization and discrimination, making them less likely to seek HIV prevention services and care for HIV, drug treatment, or other health issues[18-21]. India, similar to other LMICs, has made dramatic progress in the delivery of HIV prevention and treatment services to the general population. Consequently, overall reductions in HIV prevalence and incidence have been observed[22]. However, key populations including PWID continue to have a high burden of HIV infection. The National AIDS Control Organisation (NACO), India estimates 6%[22] of PWID are HIV-infected, while we previously found a prevalence of 18% with significant variation across cities and regions[23]. This is in stark comparison to a 0.3% prevalence among the general population[24].

Figure 1.1 HIV care continuum among 2,906 PWID in India



The HIV care continuum illustrates that the largest gap for PWID in India occurs at diagnosis, with only 43% being aware of their positive status (**Figure 1.1**)[25]. Significant attrition also occurs at the linkage to care and treatment initiation steps. HIV-infected PWID unaware of their status and/or not engaged in medical care are likely to have high viral loads, which in addition to putting their own health at risk, results in a higher likelihood of transmission of HIV to those with whom they share injecting paraphernalia and to sexual partners[26-28]. Since many PWID are

not self-referring for HIV testing and clinical care or sufficiently engaged by traditional outreach, additional strategies are needed to increase the number of diagnosed HIV-infected PWID and to achieve the UNAIDS 90-90-90 target. This would in turn lead to increased ART coverage, decreased community viral load, and, ultimately, fewer new infections[9,10,27,29,30].

Peer-based interventions

Extensive research on social networks and health has demonstrated the importance of looking beyond the individual[31-33]. Among PWID, the peer network structure and norms and characteristics of those in the network are predictive of high-risk behaviors such as unprotected sex and sharing injecting paraphernalia as well as HIV and hepatitis C virus (HCV) infection[34-41]. Among a cohort of male PWID in Chennai, prevalent HIV and HCV were associated with material support provided by network members and HCV infection was associated with having long-term active drug using network members and drug using network members being male kin[42]. Given the significant influence of networks on health and health behaviors, many have turned to using social networks to deliver interventions.

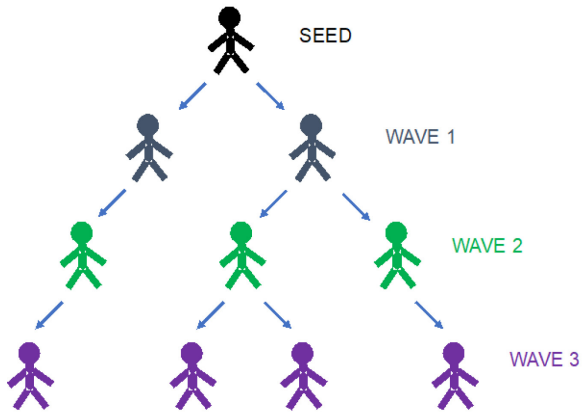
Specifically in HIV, peer driven interventions or other approaches that utilize networks to disseminate HIV prevention education through networks of PWID have been successful at decreasing risky behaviors[43-48]. In addition to interventions centered on HIV prevention, a few studies have also explored how to use peers to reach those who are HIV-infected yet unaware and hence undiagnosed[49-52]. These approaches were generally more effective at identifying new cases of HIV as compared to other strategies such as venue-based testing or self-referral; however, the majority of these studies were among MSM in urban areas in the United States[53-56].

The utilization of social networks to improve HIV care continuum outcomes among PWID or other people who use substances is not well characterized[57].

Respondent-driven sampling

Respondent-driven sampling (RDS), a chain referral method that leverages peer network connections, is now widely used in public health research, especially for HIV, for sampling hidden or difficult-to-reach populations such as PWID, MSM, and sex workers - groups for which no sampling frame exists[58,59]. Sampling begins with seeds, generally 2-10, who are influential and well-connected members of the target population. Each seed receives recruitment coupons, normally 2-5, to distribute to network members at random. Persons given coupons return to the study center with the coupon and, if eligible, are enrolled and administered a survey and complete other study procedures - this constitutes a recruitment wave. Seeds are considered wave 0, their recruits wave 1, and so on. Recruits are also given recruitment coupons to distribute to their network (**Figure 1.2)**. If recruitment is too slow or too rapid, the number of

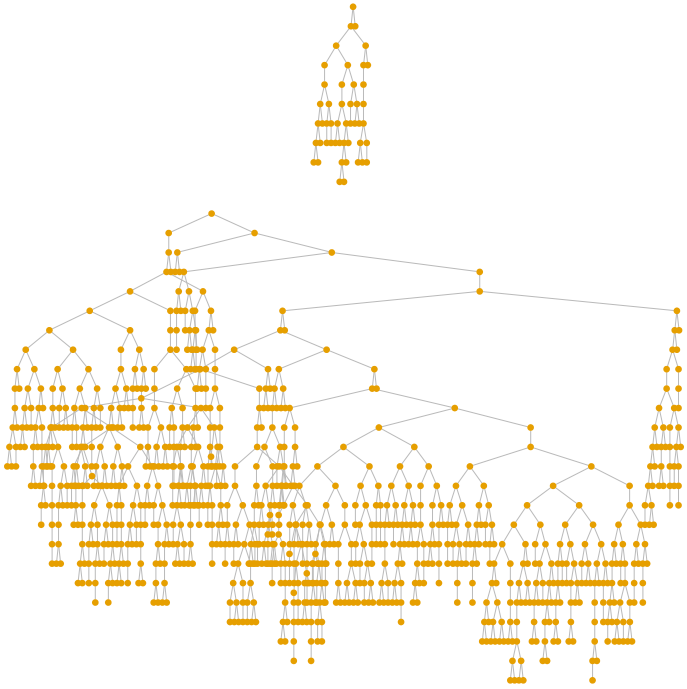
Figure 1.2 RDS recruitment example



recruitment coupons provided may be changed. There is dual compensation for RDS study participation. Study participants are provided money for participating in the study and for each

eligible person they recruit into the study. This iterative procedure continues until the desired sample size is reached (**Figure 1.3)**.

Figure 1.3 RDS recruitment tree of 1000 PWID, New Delhi, India



It should be noted that there are limitations to the RDS method and some assumptions underlying estimators for population characteristics are unlikely to be satisfied and/or difficult to assess[60-63]. New estimators for RDS data are an active area of research with newer estimators addressing common violation to assumptions. However, given appropriate conditions and after analytical correction for the sampling method, RDS can provide unbiased population estimates such as risk factors and disease burden (e.g., HIV prevalence)[58,64].

For the purposes of surveillance, RDS has proved to be an efficient strategy to recruit PWID in India, generally a more difficult population to sample given the illegal and stigmatizing nature of injection drug use. Specifically, our previous work has highlighted that RDS was able to reach undiagnosed and viremic HIV-infected PWID that had not previously been successfully engaged

by other means[65] and thus has the potential to be used as part of a service delivery model for PWID in LMICs.

GAPS IN KNOWLEDGE

Most researchers use RDS for the purposes of routine serologic and behavioral surveillance in populations for which no sampling frame exists. Recently, however, investigators have noted the promise of RDS as an implementation tool for vulnerable populations such as MSM and PWID[66-69]. Several prior RDS studies have found that PLHIV are more likely to recruit other PLHIV into an RDS[50,70] and that HIV-related characteristics (e.g., HIV testing history and diagnosis) change as recruitment progresses over time[66,71]. Therefore, the RDS recruitment process could be leveraged for the basis of an intervention in certain difficult to reach sub-groups within key populations, such as those undiagnosed and/or viremic (i.e., detectable viral load). Comparisons of RDS to traditional venue-based strategies and how best to alter this system of chain-referral to improve the identification of undiagnosed HIV-infected PWID is largely unknown, especially in the context of LMICs. Others have attempted to steer RDS recruitment to sub-groups such as younger or higher-risk PWID in the United States by increasing financial reimbursements; however, these approaches were met with mixed success[72,73]. Capitalizing on what is known about recruiters and their recruits as well other recruitment patterns provides a more specific data-driven approach to steering the RDS.

SPECIFIC AIMS AND HYPOTHESES

This research will inform the utility and implementation of an intervention strategy using RDS that seeks to improve levels of diagnosis among HIV-infected PWID. Specific aims of this dissertation are:

Aim 1: To assess the ability of RDS to reach key sub-populations of PWID (e.g., by HIV infection, diagnosis status, and socio-demographics) as compared to a venue-based strategy (integrated care centers [ICCs]).

Regression models will identify individual characteristics associated with being identified by the RDS versus an ICC. Additionally, the overall ability of RDS and ICCs to reach undiagnosed HIV-infected PWID will be summarized using the number needed to recruit (NNR). The NNR is the average number of PWID that are recruited/screened in order to find one undiagnosed HIV-infected PWID. The lower the NNR, the more efficient the strategy.

Hypothesis 1: RDS will have a lower NNR for undiagnosed PWID compared to ICCs.

Aim 2: To identify individual recruiter characteristics associated with identification of PWID via RDS who are HIV-infected and undiagnosed or viremic and identify in which settings these characteristics predict recruitment best.

Prediction models will be built to discriminate between those that do and do not recruit undiagnosed/viremic HIV infected PWID into an RDS. Areas under the receiver operating curve (AUROC) will be used to evaluate single and combinations of characteristics.

Hypothesis 2: Recruiter characteristics that will best predict identification of an undiagnosed HIV-infected PWID include: positive HIV status, daily drug injection, and a larger network size.

Aim 3: To evaluate whether the efficiency of identification of undiagnosed HIV-infected PWID can be enhanced through alterations to the RDS coupon system.

Alterations to the RDS coupon system will be evaluated in Morinda, Punjab. Specific alterations will include providing more recruitment coupons to HIV-infected PWID as compared to HIV-negative PWID; other potential recruiter characteristics that warrant additional coupons will be identified in Aim 2. Two seeds will initiate recruitment; starting at wave 1, study participants will be randomized individually in a 1:1 allocation to the normal RDS coupon system - in which all participants regardless of characteristics receive the same number of recruitment coupons - or the altered system. The number needed to recruit (NNR) for undiagnosed HIV-infected PWID will be compared between recruits of the two coupons systems.

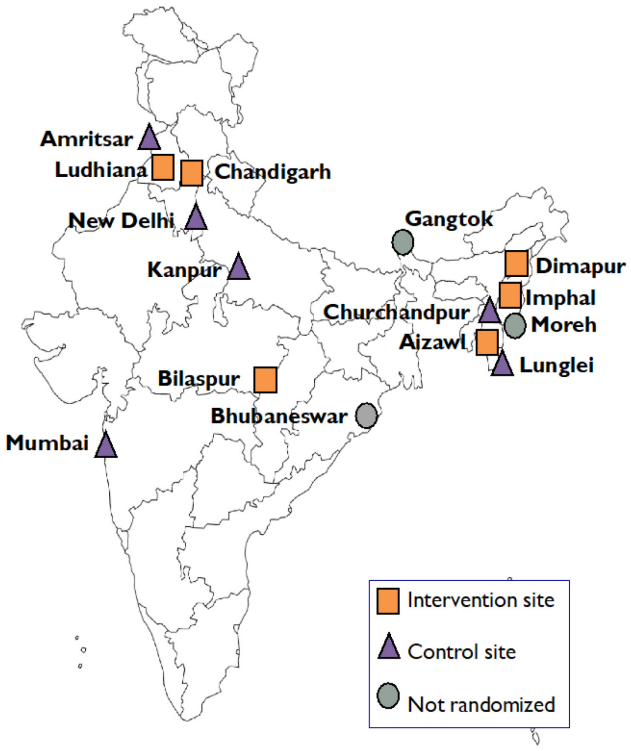
Hypothesis 3: The altered RDS approach will have a lower NNR for undiagnosed HIV-infected PWID compared to the normal RDS approach.

Data sources

This dissertation capitalizes on a large existing RDS dataset from India. Aim 1 and Aim 2 use data collected as part of a cluster-randomized trial, the National Collaboration on AIDS (NCA) trial[74]. For the baseline assessment, 15 PWID cities were included, representing 4 different stages of injection drug use (**Figure 1.4**). The Northeast (Aizawl, Churachandpur, Dimapur, Gangtok, Imphal, Ludhiana, Moreh) has the oldest, established epidemic largely due to its proximity to the

opium producing area, the 'Golden Triangle'[75]. A more recent emerging injection drug use epidemic has been documented in the North (Amritsar, Chandigarh, and Ludhiana) while little prior data exists on injection drug use in Central India (Bhubaneswar, Bilaspur, and Kanpur). Injection drug use has been observed in the large cities of Mumbai and New Delhi over the past two to three decades.

Figure 1.4 NCA Trial PWID study sites



Baseline and evaluation cross-sectional assessments used RDS to recruit PWID study participants (1000 per city). For the trial, 12 cities were selected (Bhubaneshwar, Gangtok, and Moreh were dropped) and randomized to a 1:1 allocation ratio. After the baseline assessment and randomization, ICCs - the intervention being tested - were scaled up in the six intervention cities and ran for approximately two years before initiating the evaluation RDS assessment.

Aim 3 is nested within the Reaching the Hardest of the Hard-to-reach (RHR) study, which is exploring the cost-effectiveness of RDS-based strategies at identifying PWID. One strategy being tested is the targeted time-based RDS (ttRDS), in which an RDS will run for at least one year and is evaluating the impact of varying the number of coupons for recruitment. This strategy is the focus of Aim 3 and is being conducted in Morinda, Punjab, located on the main road between Chandigarh and Ludhiana in north India.

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Chapter 2: Respondent-driven sampling is more efficient than venue-based strategies at identifying undiagnosed HIV-infected PWID in India

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ABSTRACT

Background Injection drug use drives HIV epidemics in many low-resource settings. Many people who inject drugs (PWID) are inadequately engaged in HIV services, resulting in low awareness among HIV-infected PWID. Respondent-driven sampling (RDS), a method using peer connections, is widely used in research among key populations. This study assesses the ability of RDS to identify undiagnosed HIV-infected PWID compared to a venue-based strategy in India.

Methods In six Indian cities from 2014-2017, integrated care centers (ICCs) provided PWID-tailored services such as HIV counseling/testing and needle exchange. In these same cities from 2016-2017, an RDS sample of 1000 PWID/city was conducted; RDS participants were compensated for time and referrals. Undiagnosed individuals were those who tested positive and denied a prior diagnosis. The number needed to recruit (NNR) (number screened in order to find one undiagnosed HIV-infected PWID) and the identification rate (number of undiagnosed PWID identified per week) assessed the efficiency of RDS vs. ICCs. Multinomial logistic regression was used to explore characteristics associated with identification by RDS only and RDS & ICC, both in comparison to ICC only.

Results Across the six cities, there were 10,759 ICC clients and 6,012 RDS participants; 40% of RDS participants were ICC clients (confirmed via biometrics) resulting in 14,397 unduplicated PWID, of which 753 (5%) were undiagnosed. Overall, the RDS NNR was 11 and ranged from 5 to 27 across the cities. The overall ICC NNR was 26 and ranged from 10 to 74. The NNR was lower for RDS versus the ICC overall and in all but one city. The RDS identification rate (overall: 18.6/week; cities: 1.7 to 2.8/week) was faster than the ICC identification rate (overall:

2.7/week; cities: 0.2 to 1.0/week) overall and in all cities. PWID identified by RDS vs. the ICC only were more likely to be male (adjusted odds ratios [aOR] RDS only: 6.8, both: 2.7) and HIV-infected but undiagnosed (aOR RDS only: 2.5, both: 1.5).

Conclusions In India, RDS required screening fewer PWID and more rapidly identified undiagnosed HIV-infected PWID as compared to ICCs. Network-driven recruitment strategies with moderate compensation could be considered to identify and engage groups of PWID not currently visiting venues where HIV and harm reduction services are available

INTRODUCTION

Injection drug use continues to be a driver of HIV epidemics in many settings, including low- and middle-income countries. Globally, injection drug use accounts for 30% of new infections outside of sub-Saharan Africa[1] and currently accounts for some of the fastest growing HIV epidemics globally[2]. In India, there are an estimated 1.1 million people who inject drugs[3], with growing injection drug use and HIV epidemics observed in new regions[4]. HIV prevalence in India is relatively low among the general population (0.26%[5]) while PWID experience a disproportionate burden - 6.3% being HIV-infected[6], with significant regional variation in prevalence[7].

In order to end the global HIV epidemic, UNAIDS has set the 90-90-90 target by 2020 - 90% of those HIV-infected diagnosed, 90% of those diagnosed linked to care and on sustained antiretroviral therapy (ART), and 90% of those on ART virally suppressed[8]. Importantly, these targets prioritize equity for all those effected by HIV, including key populations such as PWID who often lag behind in terms of the HIV care continuum[9]. HIV testing, medical care, and ART are provided free-of-charge by the government of India; however, utilization of services remains sub-optimal for populations like PWID due to stigma, discrimination, and accessibility[10]. We previously estimated approximately 40% of HIV-infected PWID were diagnosed[11] - well behind the UNAIDS 90% diagnosis target.

Therefore, there is an urgent need for novel strategies to reach undiagnosed HIV-infected PWID and efficiently link them to HIV testing and care services. Venue-based strategies such as testing centers and drop-in centers are frequently used to reach high-risk, stigmatized groups such as

men who have sex with men (MSM), sex workers, and PWID, and are often staffed by members of the target population and provide a safe place to deliver a variety of HIV prevention and care services specific for that population such as HIV/STI testing or referrals for appropriate testing and medical care, condoms, counseling, peer support and education. Social network-driven strategies have also been shown to be effective in reaching and engaging populations for HIV testing. Using peers to diffuse HIV prevention messages within a social network in order to change behavioral norms and reduce HIV risk has been found effective[12]. However, among PWID and other substance using populations, using social networks beyond HIV prevention, to improve steps in the HIV care continuum, has not been well-characterized[13] with few comparisons to traditional venue-based strategies.

Respondent-driven sampling (RDS) is a commonly used approach in public health for HIV surveillance and other research purposes that leverages peer network connections to sample hidden or difficult-to-reach populations such as MSM and PWID, groups for which no sampling frame exists[14]. Given a set of assumptions, estimators can be used to calculate population estimates such as HIV prevalence from the resulting sample[15], which is most often the goal of the RDS. Recently however, several studies have described the potential of using RDS or similar network-based strategies to reach those with undiagnosed, untreated, or new HIV infection[16-19]. This study assesses the ability of RDS to identify undiagnosed HIV-infected PWID compared to a venue-based strategy in India.

METHODS

Study design and procedures

Data for this study were collected for the National Collaboration on AIDS (NCA) trial (ClinicalTrials.gov identifier: NCT01686750), a cluster-randomized trial among MSM and PWID in India investigating the effectiveness of integrated care centers (ICCs) on the community uptake of HIV testing[20]. Data are restricted to the PWID stratum of the trial for this analysis. Effectiveness of the ICCs was assessed using two serial community-based cross-sectional samples before (baseline) and at least two years after implementation of ICCs (evaluation), which were established in 6 cities in India (six other cities acted as control cities for the PWID stratum of the trial). For this analysis, we utilized ICC client data from the six cities with ICCs and the evaluation RDS data from the same six cities. Three of the cities were located in the northeast of India (Aizawl, Dimapur, and Imphal), two in the north (Chandigarh and Ludhiana), and one in central India (Bilaspur).

ICCs were scaled-up and established in each city between April-July 2014 and provided PWID-focused services for approximately 2.5 years, until November 2016-February 2017. The number of ICCs established in each city was dependent on geography and the estimated size of the PWID population. One ICC was used in Aizawl, Dimapur, and Ludhiana, two were established in Bilaspur and Chandigarh (both later consolidated into one location), and three were established in Imphal. Services provided at the ICCs included HIV counseling and testing (HCT), hepatitis C antibody testing (excluding Chandigarh), syringe services (SSP), opioid agonist therapy (OAT), syndromic screening and treatment for sexually transmitted infections (STIs), condoms, tuberculosis screening, medical care and refills of antiretroviral therapy (ART) for HIV-infected clients, counseling on risk reduction (i.e., safe sex and injecting behaviors), other general health services such as blood pressure and glucose checks, and appropriate referrals. Service utilization

was voluntary and clients were not compensated for HCT or any other service utilization. A nurse and counselor were available onsite every day and a part-time physician was available on-site. Peer outreach workers encouraged PWID in the community to visit the ICC and tracked clients that needed to return for services such as a repeat HIV test. A biometric system was used to track unique clients receiving services at the ICC, the services they used, and their lab results. Clients' fingerprints were scanned then converted into unique alphanumeric codes using proprietary software; codes could not be converted back to fingerprint images. General demographics (e.g., gender, marital status, education, pin code of residence) were collected from ICC clients when they registered at their first visit. HIV testing history, risk behaviors, and diagnosis were recorded at the time of HCT. In accordance with Indian guidelines, HIV infection was assessed on-site using 3 rapid tests: Alere Deterimine 1/2 (Alere Medical, Chiba, Japan), First Response HIV Card Test 1-2.0 (Premier Medical Corporation, Daman, India), and Signal Flow Through HIV 1+2 Spot/Immunodot Test Kit (Span Diagnostics, Surat, India). Those found positive were case managed using peer health workers; more details on ICC service delivery can be found in the trial protocol paper[20].

The evaluation assessment was conducted using RDS in each of the six cities from August 2016-February 2017. Two seeds - well-connected and influential PWID in the community - were used to initiate recruitment in each city. All seeds and subsequent study participants (i.e., recruits) were given two recruitment coupons to distribute to others they knew in the community that inject drugs. Individuals that received a coupon returned to the study center, if eligible, enrolled in the study, completed study procedures, and received two recruitment coupons to distribute to their network at random. Coupons had a bar-code to link recruiters and recruits as well as a

hologram to prevent duplication. Recruitment continued until the desired sample size was met - 1000 in each city. Eligibility criteria to enroll in the RDS included (1) being at least 18 years old, (2) provision of informed consent, (3) possession of a valid coupon unless a seed, and (4) self-reported injection drug use in the prior 24 months. Compensation was provided for study participation (US $3.8 [INR 250]) and for each recruit participants referred that enrolled in the study (US $0.80 [INR 50]/recruit, up to two total). The same biometric system was used to track duplicate enrollment of participants and to link study participants that were also ICC clients. After informed consent, RDS participants provided a blood sample and completed an interviewer-administered questionnaire with modules on socio-demographics, network characteristics, injection and sexual risk behaviors, harm reduction service use, and HIV testing and care history. All participants underwent HIV counseling and testing using 3 rapid tests (as described previously in the ICCs) with appropriate referrals for medical care for those that tested positive. Importantly, all RDS procedures were carried out at a discrete study venue that was not associated with the ICC.

Statistical methods

The main outcome of interest is the approach that identified PWID from the community - the ICC or RDS. For exploratory data analysis and regression modeling, a pooled data set was created containing ICC client data from the six cities and the evaluation RDS sample from these same cities. Using the biometric data, we classified individuals in the pooled data as being identified by the ICC only (i.e., were ICC clients and no RDS participants had matching fingerprint data), identified by the RDS only (i.e., were sampled into the RDS with no fingerprint match to an ICC client), or identified by both the ICC and RDS (i.e., were RDS participants and

had matching fingerprints to an ICC client). Exploratory data analysis included the frequency/percentage and median/interquartile range (IQR) of characteristics by identification approach and chi-squared or Kruskal-Wallis tests were used for statistical comparison across categories and continuous characteristics, respectively. Correlates of identification by approach were explored using multinomial logistic regression with the ICC only group as the reference condition. Thus, odds ratios (ORs) for identification by RDS only and both ICC and RDS are compared to PWID that were ICC clients only.

The main characteristic of interest was undiagnosed HIV infection defined as PWID who tested positive either at the ICC or RDS but did not report a prior diagnosis. For exploratory data analysis, individuals were also further categorized as HIV negative, HIV-infected and previously diagnosed, and having an unknown status. ICC clients could voluntarily request HCT services at the ICC at any time. A number of clients, especially those that visited the ICC infrequently, did not undergo HCT and did not have a record of HIV-specific care (i.e., CD4 count, ART registration number or refill information); therefore, their HIV status was classified as unknown. Clients who did not have a positive HIV test result at the ICC but reported a prior HIV diagnosis to the counselor or had a record of HIV care at the ICC were considered to be previously diagnosed. RDS study participants who had a positive test at the study visit and reported a prior diagnosis were considered to be previously diagnosed. HIV negative PWID were those with an HIV negative test either at the ICC or the RDS study visit. Since all RDS participants underwent HIV counseling and testing regardless of self-reported status and completed a questionnaire as part of the study procedures, all RDS participants had complete data on current HIV infection and diagnosis status, with the exception of three that had a missing infection status. Other

correlates investigated included basic socio-demographics (i.e., city, age, gender, marital status, and educational attainment), which were available for both ICC clients and RDS participants.

To summarize the efficiency of ICCs and RDS in identifying undiagnosed HIV-infected PWID, we used two different measures: (1) the number needed to recruit (NNR) which is the number needed to recruit/screen in order to find one undiagnosed individual (total number of ICC clients or RDS participants / number of undiagnosed PWID identified) and (2) the identification rate which is the number of undiagnosed individuals identified per week (number of undiagnosed PWID identified / number of weeks ICC provided services or RDS recruitment was active). The lower the NNR, the more efficient an approach and the higher the rate, the more efficient an approach. The NNR and identification rate were calculated independently for the ICC client data set and RDS data set, for each city individually and pooled with all six cities. Calculation of the NNR and identification rate for the RDS excluded seeds and the first two waves of recruitment (n=71) to be consistent with the confidence interval calculation described below.

Confidence intervals around the NNR were calculated using a bootstrap method for both the ICC and RDS data. For the ICC, 1000 samples with replacement of the ICC client data were taken and the NNR calculated for each sample. The 2.5^{th} and 97.5^{th} percentiles of the 1000 NNR estimates represent the 95% confidence interval. For the RDS, a sample with replacement of only the third wave of recruitment was conducted. For each individual sampled in wave 3, all their descendants (i.e., all recruits below them in the recruitment tree) were selected; the NNR was calculated. This process was repeated 1000 times and the 2.5^{th} and 97.5^{th} percentiles of the 1000 NNR estimates represent the 95% confidence interval for the RDS NNR. Confidence intervals

for the ICC identification rate were exact Poisson confidence intervals. For the RDS, 95% confidence intervals around the identification rate were calculated in the same manner as the NNR with 1000 bootstrapped samples from wave 3 individuals with their descendants. The NNR/identification rate difference between the ICC and RDS was calculated by subtracting the RDS point estimate from the ICC point estimate; 95% confidence intervals around the difference were calculated using a bootstrap method similar to the confidence interval method described above for the NNR and rate using 1000 bootstrapped samples.

Trends over time in the NNR and identification rate were examined using exploratory methods for the ICC and RDS data separately, for each city individually and all six cities pooled. Specifically, the NNR and rate were calculated for each week the ICC provided services/RDS recruitment was active. The first HIV test date or first ICC visit for those that never received an HIV test in the ICC were used for the ICC graph; the study visit date was used for the RDS graph.

As a sensitivity analysis for the NNR and identification rate among ICC clients, the sample was restricted to the first 1000 clients to match the sample size of RDS participants in each city. The NNR and identification rate were re-calculated for the ICC with this restricted sample. For RDS data, a sensitivity analysis was conducted in which HIV-infected PWID who self-reported not previously being aware of their infection but had a suppressed viral load (<150 copies/mL) were reclassified as previously diagnosed since they were likely on antiretroviral therapy (n=90); the NNR and identification were then re-calculated. Viral load was very rarely available for ICC

clients since monitoring is not the standard of care for patients and therefore re-classification of diagnosis status based on viral load was not possible for ICC clients.

All analyses were conducted using Stata (StataCorp. 2017. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC). P-values were considered statistically significant at <0.05.

To visualize the geographic reach of the ICC and RDS approaches, we mapped the pin code (similar to a US zip code) of residence for ICC clients only, RDS participants only, and both ICC clients and RDS participants in one city, Ludhiana. Ludhiana is represented by a larger number of pin codes in comparison to the smaller northeast/central cities and had more valid/known pin codes in the data, thus allowing for better differentiation for mapping the two approaches. PWID with unknown or invalid pin codes were dropped from the mapping analysis. For each individual, the geodesic distance (i.e., as the crow flies) in kilometers (km) was calculated from their pin code of residence centroid to the ICC or RDS address using latitude and longitude for both points. For persons that were both ICC clients and RDS participants the longest distance (either to the ICC or RDS site) was used. Mean (standard deviation [SD]) distances from the residence centroid to the ICC/RDS site were compared with a one-way ANOVA to test for significant differences across the three categories of PWID. Outliers, distances greater than 100km (n=7), were dropped from analyses. Distances were calculated and maps were created using ArcGIS version 10.2 (Redlands, CA, US) using OpenStreetMap as the base layer (OpenStreetMap contributors, under the Open Database License, for which terms are available at http://opendatacommons.org/licenses/odbl/1.0/).

Ethical clearances

This study was approved by the institutional review boards of Johns Hopkins Medicine and the Y.R. Gaitonde Centre for AIDS Research and Education.

RESULTS

There was a total of 10,759 ICC clients and 6,012 RDS study participants. After evaluating overlap in the two approaches, nearly 40% of RDS participants were also ICC clients resulting in 14,397 unique PWID; 8385 (58.2%) were ICC clients only, 3638 (25.3%) were RDS participants only, and 2374 (16.5%) were both ICC clients and RDS participants. Median age of the sample was 29 (interquartile range [IQR]: 24-36), 10.4% were women, 46.8% were currently married, and 82.9% completed at least secondary level education. Overall, 71.4% were HIV negative, 5.2% were HIV-infected but undiagnosed, 12.6% were HIV-infected and previously diagnosed, and 10.8% had an unknown HIV status.

Socio-demographics and HIV infection/diagnosis significantly differed across the three identification approaches (**Table 2.1**). ICC clients were more likely to be women (15.1% vs. 3.4% and 4.8% for RDS only and both ICC and RDS, respectively). RDS participants were more likely to be widowed/divorced/separated (10.0% vs. 6.1% and 5.1% for ICC only and both ICC and RDS, respectively), to have completed a high school education or more (24.1% vs. 15.2% and 13.0%), and to be HIV-infected but undiagnosed (9.4% vs. 3.4% and 5.4%).

In multivariable analysis adjusted for socio-demographics and HIV infection/diagnosis status, these differences persisted (**Table 2.2**). Men were nearly 7 times more likely to be sampled by the RDS only (adjusted odds ratio [aOR]: 6.84, 95% confidence interval [CI]: 5.61 - 8.35) and nearly 3 times more likely to be both ICC clients and RDS participants (aOR: 2.72, 95% CI: 2.21 - 3.35) compared to ICC clients only. Widowed/divorced/separated PWID had 2 times higher odds of being in the RDS only (aOR: 2.03, 95% CI: 1.71 - 2.40). PWID with at least a high school education had 1.75 times higher odds of being in the RDS only (aOR: 1.75, 95% CI: 1.54 - 2.00). RDS participants and both ICC clients and RDS participants had 2.5 times and 1.5 times higher odds of being HIV-infected but undiagnosed, respectively, compared to ICC clients only (aOR: 2.46, 95% CI: 2.07 - 2.93 and aOR: 1.52, 95% CI: 1.22 - 1.90).

Number needed to recruit (NNR)

The overall NNR for the ICC was 26.1 (95% CI: 23.8 - 28.8) and for the RDS was 10.9 (9.2 - 13.2), implying on average the ICC required screening 26 PWID in order to find one undiagnosed individual while the RDS required screening 11 to find one undiagnosed individual (**Figure 2.1**). Stratified by city, the ICC NNR ranged from 10.2 to 73.5 and the RDS NNR ranged from 4.5 to 27.4. The NNR for RDS was markedly lower than the ICC overall and in all cities, with the exception of Bilaspur. The difference between the ICC and RDS ranged from 7.2 to 54.1 (excluding Bilaspur) additional individuals needed to be screened in the ICC for one additional undiagnosed PWID, with lowest lower bound of the 95% CI of 4.1 (**Supplementary Table 2.1**).

The NNR over time for the ICCs (pooling all six cities) did not indicate a specific temporal or seasonal pattern (**Figure 2.2a**), rather it appears somewhat stable with peaks appearing at random times. The ICC NNR also appears stable over time when stratified by city (**Supplementary Figures 2**). The NNR for the RDS (pooling all six cities) indicates a slow steady increase over weeks of recruitment (**Figure 2.2b**). However, when stratified by city, the patterns vary (**Supplementary Figures 2**); in some cities, there is a suggestion of an increase in the RDS NNR over time (Aizawl, Bilaspur, Imphal) while others appear to decrease over time (Chandigarh, Dimapur) or have no identifiable pattern (Ludhiana).

Identification rate

The overall identification rate per week for the ICC was 2.7/week (95% CI: 2.5 - 3.0) and for the RDS was 18.6/week (95% CI: 14.0 - 24.1) (**Figure 2.3**). By city, the ICC rate ranged from 0.2 to 1.0 and the RDS rate ranged from 1.7 to 16.0. The identification rate was meaningfully higher for RDS than the ICC overall and in all cities. The rate difference between the ICC and RDS by city ranged from 1.5 to 15.1/week additional undiagnosed PWID identified by the RDS. (**Supplementary Table 2.1**).

Similar to the NNR, the identification rate over time for the six pooled ICCs appears somewhat stable over time with peaks at random times (**Figure 2.2c**). For the Aizawl ICC, the rate appears higher in the later weeks while for Bilaspur, the rate appears higher in the earlier weeks; otherwise, the other ICC city-specific identification rates appear stable over time (**Supplementary Figures 2**). The identification rate for the RDS indicates a sharp increase in the first several weeks then a slow steady decrease (**Figure 2.2d**). Aizawl, Bilaspur, and Imphal

RDS show a similar pattern (decreasing rate over time); however, the other city-specific rates are more erratic with no clear pattern (**Supplementary Figures 2**).

NNR and identification rate sensitivity analyses

When restricting to the first 1000 ICC clients, the overall ICC NNR decreased (26.1 to 23.1) (**Supplementary Table 2.2**) and in each city the NNR was slightly lower or similar, with the exception of Aizawl in which the NNR increased substantially (11.7 to 17.5). The NNR difference between the ICC and RDS generally decreased but remained meaningful with the exception of Bilaspur. The identification rate was lower when restricting to the first 1000 ICC clients, overall (2.7 to 1.7/week) and in each city. The rate difference between the ICC and RDS increased slightly and remained markedly different.

After re-classifying undiagnosed RDS participants with undetectable viral loads, the RDS NNR increased, overall (10.9 to 13.1) (**Supplementary Table 2.3**) and in each city. The NNR difference between the ICC and RDS decreased slightly but remained meaningful, with the exception of Ludhiana (difference: 4.2, 95% CI: -4.3 to 10.7). For the RDS NNR over time, the pattern remained the same - increasing over weeks of recruitment - after reclassification (**Figure 2.2b**). The overall RDS identification rate decreased (18.6 to 15.5) and in each city the rate was lower or similar. The rate difference between the ICC and RDS decreased but remained large. For the identification rate over time, the pattern remained the same - a sharp increase in the first several weeks followed by a slow steady decrease - after reclassification (**Figure 2.2d**).

Geographic reach of ICC and RDS

In Ludhiana, 9.3% of PWID did not know their pin code of residence or reported an invalid pin code. However, this was differential by group: 11.5% among ICC clients only, 0.3% among RDS participants only, and 16.9% among both ICC clients and RDS participants. Pin code maps of ICC clients and RDS participants in Ludhiana (**Figure 2.4**) indicate that PWID who were ICC clients only or both ICC clients and RDS participants generally lived closer to the city center (nearer to both the ICC and RDS site). In comparison, more PWID who were RDS study participants came from areas farther from the city center. The mean distance between an RDS participant's pin code and the RDS site (11.2 km, SD: 10.8 km) was significantly higher ($p<0.001$) than the mean distance for ICC clients (7.5 km, SD: 4.6 km) and those that were both ICC clients and RDS participants (9.2 km, 4.4 km).

DISCUSSION

As compared to ICCs - a venue-based strategy - RDS required screening fewer PWID and more rapidly identified undiagnosed HIV-infected PWID. On average, RDS screened 15 fewer PWID in order to identify one undiagnosed PWID and identified nearly 16 more undiagnosed PWID each week compared to ICCs. These meaningful differences were seen in all six cities individually, with the exception of the NNR in Bilaspur. Additionally, population demographics varied across the strategies; men, those widowed/divorced/separated, and with higher education were more likely to be RDS participants than ICC clients. In one city where we were able to map area of residence, the data suggests that RDS reaches PWID that live farther from the RDS study site while ICC clients generally reside closer to the ICC in the central area of the city.

Other investigations of the ability of RDS to identify undiagnosed people living with HIV (PLWH) compared to other strategies have found similar results. A study by Gwadz and colleagues found that among high-risk heterosexuals in New York City, RDS yielded significantly more individuals with newly diagnosed HIV as compared to venue-time-based sampling from commercial areas[21]. Kan and colleagues compared RDS, both with and without restricting recruitment waves based on HIV status, to peer community outreach among PWID in several different areas in Tajikistan and found those recruited through RDS were more likely to be new positives than the outreach strategy[22]. However, not all studies have found an improved efficiency associated with RDS. Among people who used crack in San Salvador, Glasman and colleagues found a similar percentage of new HIV diagnoses among testers in a self-referral and peer-referral period, both lasting 14 months, though the absolute number of new diagnoses was nearly twice as high in the peer-referral time period[23]. Among African American MSM in Baltimore, a social network strategy very similar to RDS was used in which HIV-infected MSM recruited social network members[24]. Ellen and colleagues found that this network strategy as well as testing partners of HIV-infected persons found no new HIV positives while a venue-based strategy identifying MSM from areas where they socialize and meet new sex partners yielded about 10% new diagnoses. Importantly, in this network strategy, only HIV-infected MSM were able to recruit others which is a key departure from the typical way in which RDS is conducted. Therefore, the effectiveness of RDS to identify undiagnosed PLWH may differ across populations and contexts when compared to other common strategies that are employed such as community outreach, partner testing, or venue/clinic-based strategies.

While RDS was overall more efficient in identifying undiagnosed HIV-infected PWID than the ICCs, an ideal scenario would employ both approaches to ensure that progress is made along the entire HIV continuum, not just the first step, and addresses prevention needs. PWID that are HIV negative require continued engagement with counseling, support, and access to harm reduction and other HIV prevention services to remain uninfected. Additionally, HIV-infected PWID once diagnosed need immediate linkage to care and treatment with potentially many decades of medical care and ART support. While RDS can quickly identify undiagnosed PLWH, ICCs or similar venue- or clinic-based settings provide other vital services. Importantly, for populations such as PWID that often experience stigma and discrimination while accessing services, settings like ICCs offer a safe space specifically tailored for them. Additionally, ICCs were more likely to identify women who inject drugs compared to the RDS, possibly due to different network characteristics than men. Women are a particularly vulnerable sub-group of PWID in India[7,25,26] and any interventions or approaches that successfully engage them in HIV-related prevention and care should be promoted.

There are several limitations to this work that should be noted. For the main analysis, awareness of HIV-positive status was self-reported in the RDS and ICC data which is subject to recall or reporting bias. A sensitivity analysis in which RDS participants with suppressed viral load but did not report a prior diagnosis were reclassified as previously diagnosed did not change the overall inference that RDS was more efficient than the ICCs. However, since viral load was not routinely collected from ICC clients, this sensitivity analysis is restricted to only RDS participants. The two approaches explored - the RDS and ICCs - did not run completely concurrently. The RDS period fully overlapped with the provision of services by ICCs in each

city but ICCs began approximately two years before the evaluation RDS was initiated. Temporal changes and population migration could have occurred changing risk behaviors and/or population characteristics. Lastly, inherent to most RDS studies, monetary compensation is provided to study participants for completing study procedures and successfully recruiting other eligible study participants into the study; use of ICC services was not compensated. We are unable to separate out the effect of a network-driven strategy and compensation within the RDS on its efficiency and how that may affect its efficiency in relation to the ICCs.

In summary, the ability of RDS to more efficiently identify undiagnosed HIV-infected PWID compared to ICCs in India suggests that similar network-driven strategies with minimal compensation could be used to identify and engage groups not currently visiting venues or clinics for HIV prevention and care services. Given the very fast approaching deadline for the UNAIDS 90-90-90 target, finding and implementing effective and efficient methods to improve HIV diagnosis, treatment initiation, and viral suppression for all populations affected by HIV, especially key populations such as PWID, is critical.

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Table 2.1 Socio-demographic characteristics and HIV status by identification approach among PWID in India

Characteristic n (column %)/median (IQR)	**Identified by ICC only (N=8385)**	**Identified by RDS only (N=3638)**	**Identified by both ICC and RDS (N=2374)**	**p-value[1]**
City				
Aizawl	1260 (15.0)	742 (20.4)	260 (11.0)	
Dimapur	1474 (17.6)	835 (23.0)	167 (7.0)	
Imphal	2751 (32.8)	446 (12.3)	556 (23.4)	<0.001
Bilaspur	581 (6.9)	492 (13.5)	510 (21.5)	
Chandigarh	974 (11.6)	489 (13.4)	513 (21.6)	
Ludhiana	1345 (16.0)	634 (17.4)	368 (15.5)	
Age	29 (25 - 36)	28 (23 - 35)	29 (24 - 36)	<0.001
Gender				
Man	7121 (84.9)	3515 (96.6)	2260 (95.2)	<0.001
Woman	1263 (15.1)	123 (3.4)	113 (4.8)	
Transgender/*hijra*	1 (0.01)	0 (0)	0 (0)	
Marital status				
Never married	3809 (45.4)	1746 (48.0)	1176 (49.6)	<0.001
Married/long-term partner/living with partner	4065 (48.5)	1527 (42.0)	1077 (45.4)	
Widowed/divorced/separated	511 (6.1)	365 (10.0)	120 (5.1)	
Educational attainment				
Primary or less	1620 (19.3)	927 (25.5)	504 (21.2)	<0.001
Secondary school	5490 (65.5)	1834 (50.4)	1561 (65.8)	
High school or above	1275 (15.2)	877 (24.1)	308 (13.0)	
HIV/diagnosis status				
Negative	5542 (66.1)	3069 (84.4)	1662 (70.0)	<0.001
Positive, undiagnosed	283 (3.4)	341 (9.4)	129 (5.4)	
Positive, previously diagnosed	1156 (13.8)	227 (6.2)	434 (18.3)	
Unknown status	1404 (16.7)	1 (0.03)	149 (6.3)	

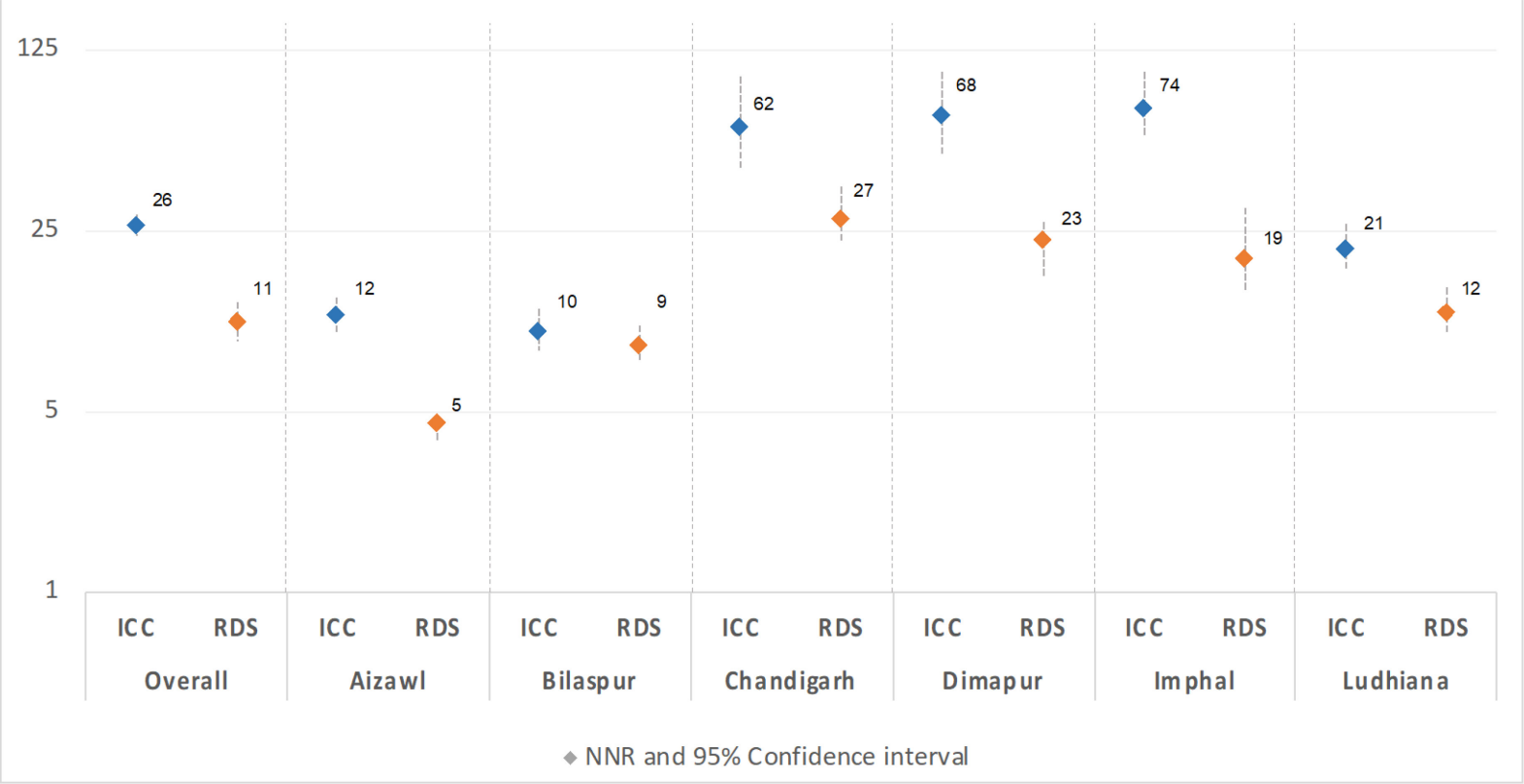
PWID: people who inject drugs; IQR: interquartile range; ICC: integrated care clinic; RDS: respondent-driven sampling
1: Chi-square test for categorical characteristics and Kruskal-Wallis test for continuous characteristics

Table 2.2 Correlates of identification by RDS only and both ICC and RDS as compared to ICC only among PWID in India

Correlate	RDS only OR	95% CI	Both ICC and RDS OR	95% CI	RDS only aOR[1]	95% CI	Both ICC and RDS aOR[1]	95% CI
City								
Aizawl	Reference		Reference		Reference		Reference	
Dimapur	0.96	0.85 - 1.09	0.55	0.45 - 0.68	1.32	1.15 - 1.53	0.65	0.52 - 0.81
Imphal	0.28	0.24 - 0.32	0.98	0.83 - 1.15	0.27	0.23 - 0.31	0.94	0.79 - 1.11
Bilaspur	1.44	1.24 - 1.67	4.25	3.56 - 5.09	1.45	1.23 - 1.70	4.08	3.38 - 4.92
Chandigarh	0.85	0.74 - 0.98	2.55	2.15 - 3.03	0.91	0.78 - 1.06	2.49	2.08 - 2.98
Ludhiana	0.80	0.70 - 0.91	1.33	1.11 - 1.58	0.85	0.74 - 0.98	1.34	1.12 - 1.61
Age, by 10-year increase	0.87	0.85 - 0.93	0.95	0.90 - 1.00	0.96	0.90 - 1.02	1.07	1.01 - 1.15
Men (vs. women)[2]	5.07	4.19 - 6.13	3.55	2.91 - 4.32	6.84	5.61 - 8.35	2.72	2.21 - 3.35
Marital status								
Married/long-term partner/living with partner	Reference		Reference		Reference		Reference	
Never married	1.22	1.12 - 1.32	1.17	1.06 - 1.28	0.99	0.90 - 1.09	1.06	0.95 - 1.18
Widowed/divorced/separated	1.90	1.64 - 2.20	0.89	0.72 - 1.09	2.03	1.71 - 2.40	1.22	0.95 - 1.18
Educational attainment								
Primary or less	Reference		Reference		Reference		Reference	
Secondary school	0.58	0.53 - 0.64	0.91	0.81 - 1.03	0.69	0.62 - 0.77	1.01	0.89 - 1.14
High school or above	1.20	1.07 - 1.35	0.78	0.66 - 0.91	1.75	1.54 - 2.00	0.92	0.78 - 1.09
HIV/diagnosis status								
Negative								
Positive, undiagnosed	Reference	1.85 - 2.56	Reference		--	--	--	--
Positive, previously	2.18	0.31 - 0.41	1.52	1.23 - 1.89				
diagnosed	0.35	0.0002 -	1.25	1.11 - 1.42				
Unknown status	0.001	0.01	0.35	0.30 - 0.42				
Undiagnosed HIV positive	2.96	2.52 - 3.48	1.65	1.33 - 2.04	2.46	2.07 - 2.93	1.52	1.22 - 1.90

RDS: respondent-driven sampling; ICC: integrated care clinic; PWID: people who inject drugs; OR: Odds ratio from multinomial logistic regression, reference outcome is identification by ICC only; CI: confidence interval;
1: Adjusted for all other covariates in table; 2: Transgender/*hijra* individual dropped from model

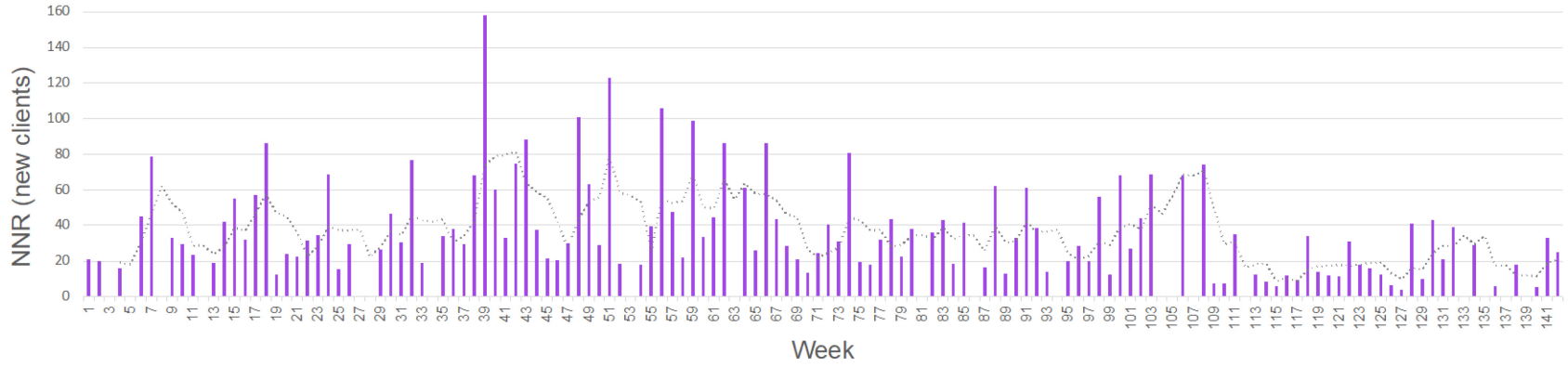
Figure 2.1 Number needed to recruit (NNR) for undiagnosed HIV-infected PWID, stratified by city and strategy



	Overall	Aizawl	Bilaspur	Chandigarh	Dimapur	Imphal	Ludhiana
HIV prev.	20.5	23.8	18.8	5.6	15.7	21.2	22.0
HIV inc.	5.2	14.1	4.8	1.7	0.9	0	6.0

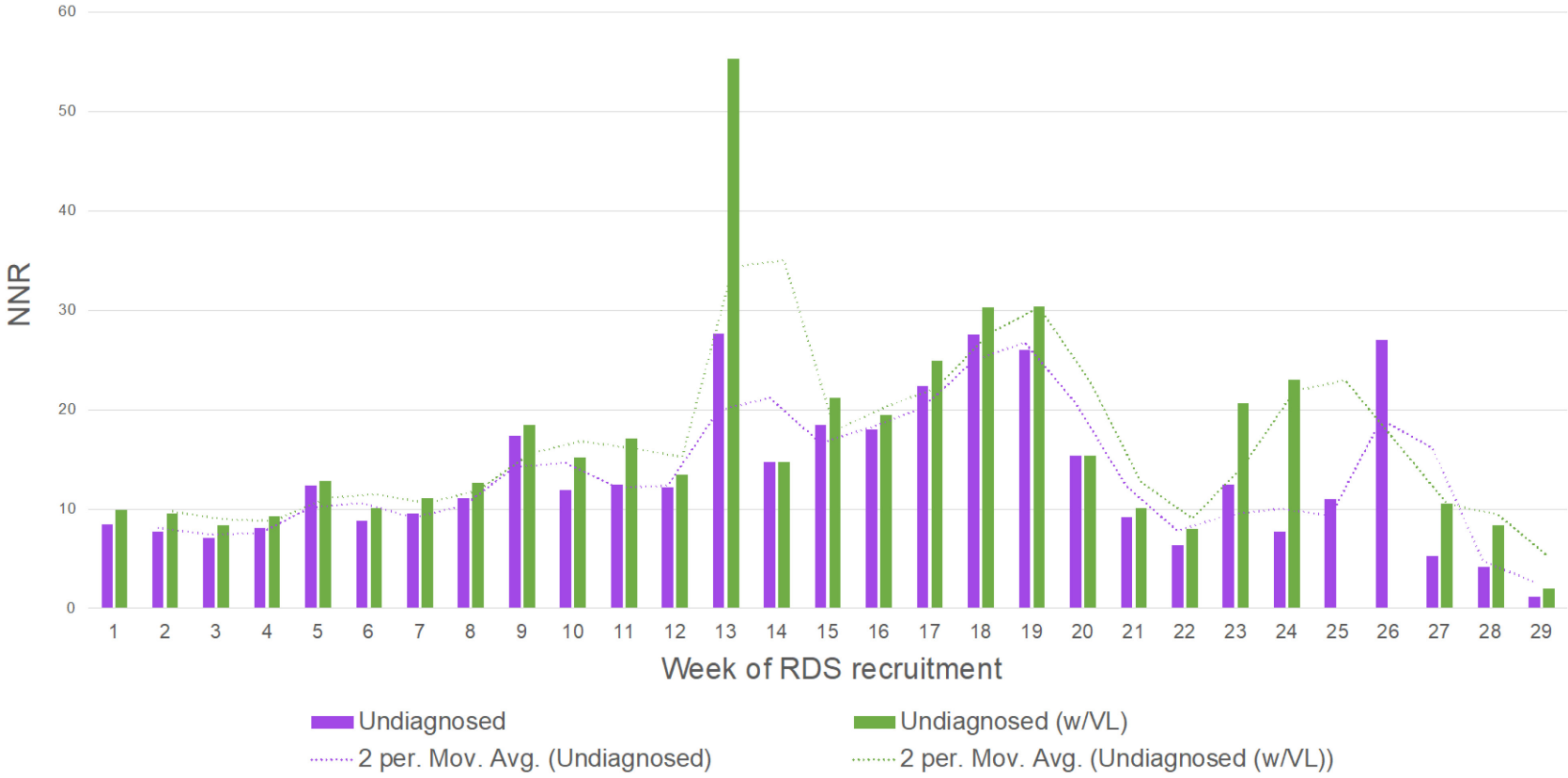
ICC: integrated care center; RDS: respondent-driven sampling; prev.: prevalence from RDS, RDS weighted; inc.: annual cross-sectional incidence estimate from RDS
Y-axis is *ln* transformed

Figure 2.2a NNR for undiagnosed HIV-infected PWID in India by week at the ICCs



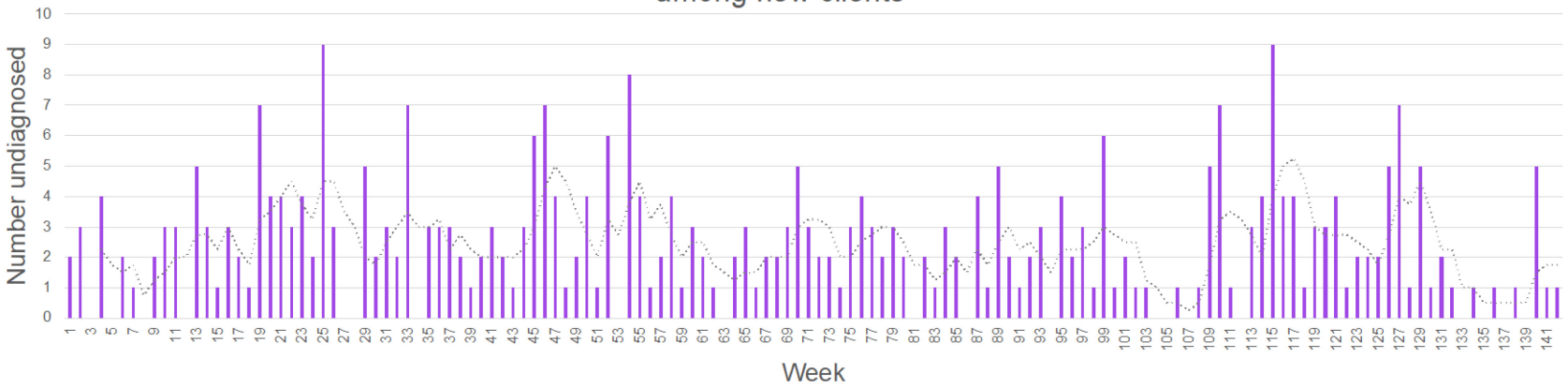
NNR: number needed to recruit; PWID: people who inject drugs; ICC: integrated care center; Weeks with no bar indicate no undiagnosed individuals were identified in that week, resulting in an undefined NNR

Figure 2.2b NNR for undiagnosed HIV-infected PWID in India over weeks of RDS recruitment



NNR: number needed to recruit; PWID: people who inject drugs; RDS: respondent-driven sampling; VL: reclassified using viral load
Weeks with no bar indicate no undiagnosed individuals were identified in that week, resulting in an undefined NNR

Figure 2.2c Number undiagnosed HIV-infected PWID in India identified by week at the ICCs, among new clients

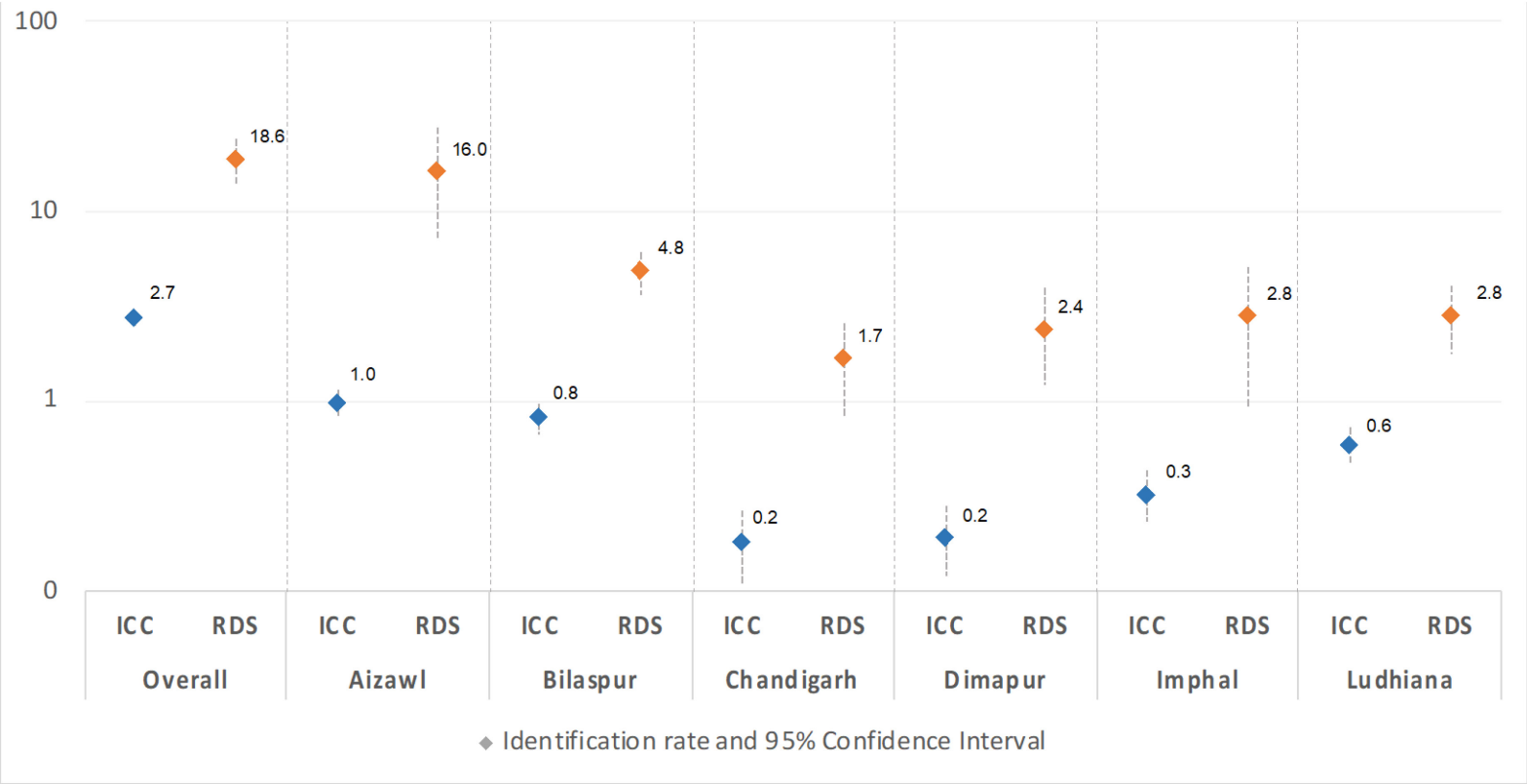


PWID: people who inject drugs; ICC: integrated care center

Figure 2.2d Number of undiagnosed HIV-infected PWID identified each week of RDS recruitment

PWID: people who inject drugs; RDS: respondent-driven sampling; VL: reclassified using viral load

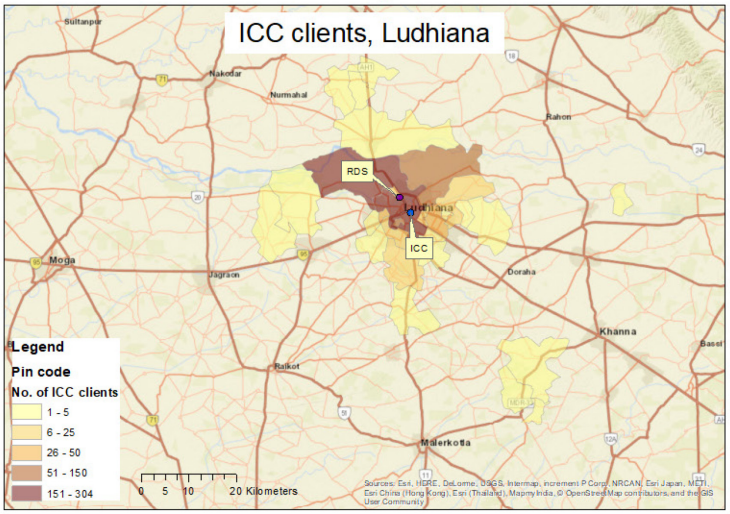
Figure 2.3 Identification rate per week for undiagnosed HIV-infected PWID, stratified by city and strategy

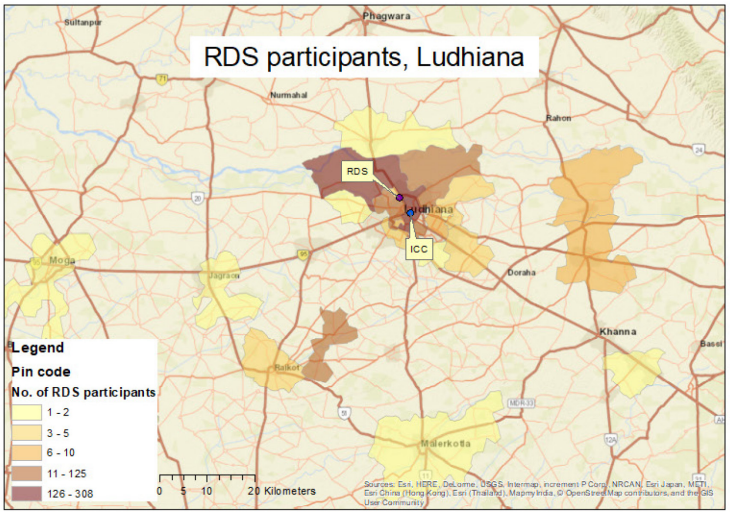


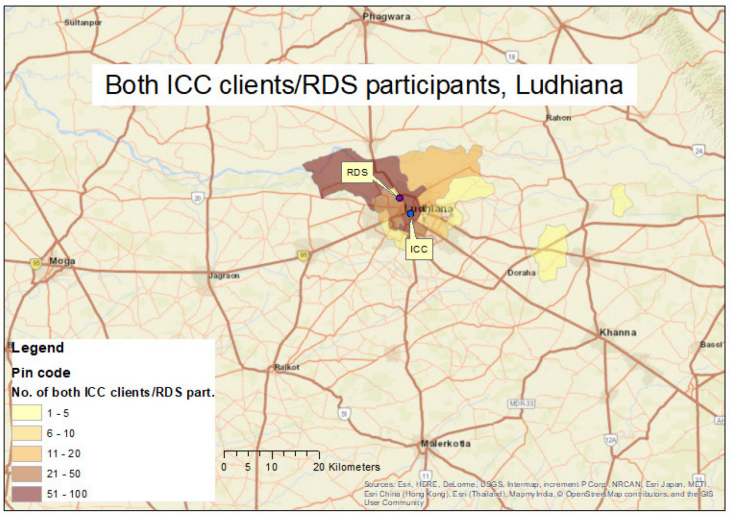
	Overall	Aizawl	Bilaspur	Chandigarh	Dimapur	Imphal	Ludhiana
HIV prev.	20.5	23.8	18.8	5.6	15.7	21.2	22.0
HIV inc.	5.2	14.1	4.8	1.7	0.9	0	6.0

ICC: integrated care center; RDS: respondent-driven sampling; prev.: prevalence from RDS, RDS weighted; inc.: annual cross-sectional incidence estimate from RDS
Y-axis is *ln* transformed

Figure 2.4 Pin code of residence among ICC clients and RDS participants, Ludhiana, India







ICC: integrated care center; RDS: respondent-driven sampling
call-outs indicate ICC and RDS site locations

Supplementary Table 2.1 Number needed to recruit (NNR) and identification rate difference between ICC and RDS, overall and by city

	NNR difference[1]	95% CI	Identification Rate difference[1]	95% CI
Overall	15.2	12.0 - 18.4	-15.9	-21.5, -11.4
Aizawl	7.2	5.4 - 9.7	-15.1	-25.9, -6.43
Dimapur	45.4	24.8 - 87.5	-2.2	-3.9, -1.0
Imphal	54.1	35.6 - 81.7	-2.5	-5.0, -0.6
Bilaspur	1.2	-1.3 - 3.7	-4.0	-5.2, -2.9
Chandigarh	34.6	14.6 - 72.2	-1.5	-2.4, -0.7
Ludhiana	8.9	4.1 - 14.0	-2.3	-3.5, -1.2

1: RDS estimate subtracted from ICC estimate
ICC: Integrated care clinics; RDS: respondent-driven sampling
NNR: Average number of people who inject drugs (PWID) recruited/screened in order to identify one undiagnosed HIV-infected PWID
Identification rate per week: Average number of undiagnosed PWIED identified per week

Supplementary Table 2.2 Number needed to recruit (NNR) and identification rate per week for undiagnosed HIV-infected PWID restricted to the first 1000 ICC clients, overall and by city

	NNR	95% CI	Identification Rate	95% CI
Overall	23.1	20.6 - 26.2	1.7	1.5 - 1.9
Aizawl	17.5	14.1 - 23.3	0.4	0.3 - 0.6
Dimapur	55.6	37.0 - 90.9	0.1	0.1- 0.2
Imphal	71.4	45.5 - 142.9	0.1	0.05 - 0.2
Bilaspur	9.9	8.3 - 12.1	0.8	0.6 - 0.9
Chandigarh	45.5	32.3 - 76.9	0.2	0.1 - 0.3
Ludhiana	20.8	16.4 - 27.8	0.3	0.3 - 0.5

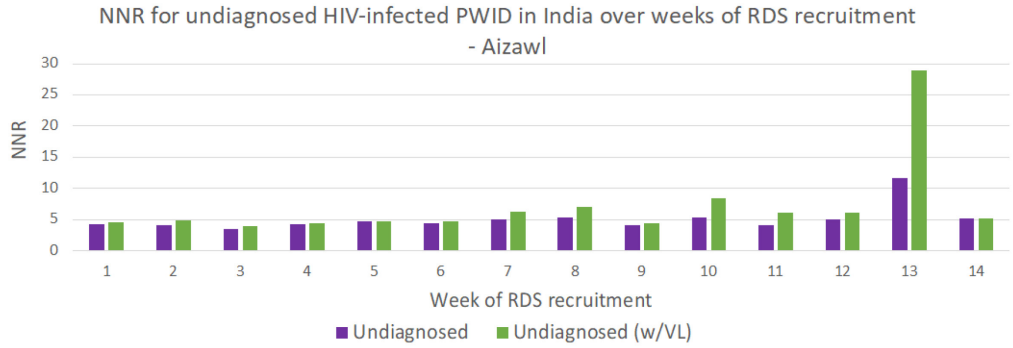
ICC: Integrated care clinics
NNR: Average number of people who inject drugs (PWID) recruited/screened in order to identify one undiagnosed HIV-infected PWID
Identification rate per week: Average number of undiagnosed PWIED identified per week

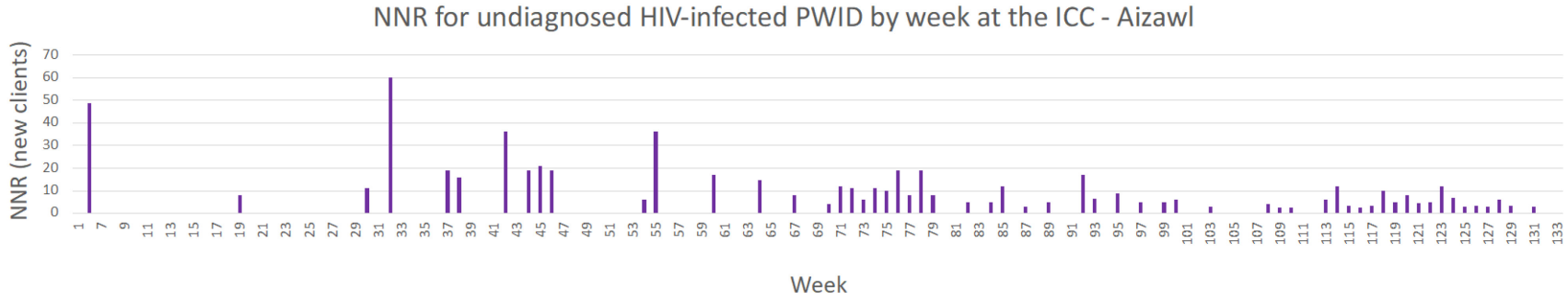
Supplementary Table 2.3 Number needed to recruit (NNR) and identification rate per week for undiagnosed HIV-infected PWID in the RDS after re-classification of self-reported undiagnosed HIV-infected PWID with undetectable viral loads

	NNR	95% CI	Identification Rate	95% CI
Overall	13.1	11.1 - 15.6	15.5	11.6 - 20.6
Aizawl	5.3	4.3 - 5.9	13.5	6.4 - 22.2
Dimapur	26.0	17.3 - 31.5	2.1	1.2 - 3.4
Imphal	28.2	21.2 - 41.2	1.9	0.7 - 3.5
Bilaspur	9.8	8.3 - 11.8	4.5	3.5 - 5.5
Chandigarh	28.2	23.5 - 39.4	1.6	0.8 - 2.6
Ludhiana	16.7	13.0 - 24.8	2.0	1.0 - 3.1

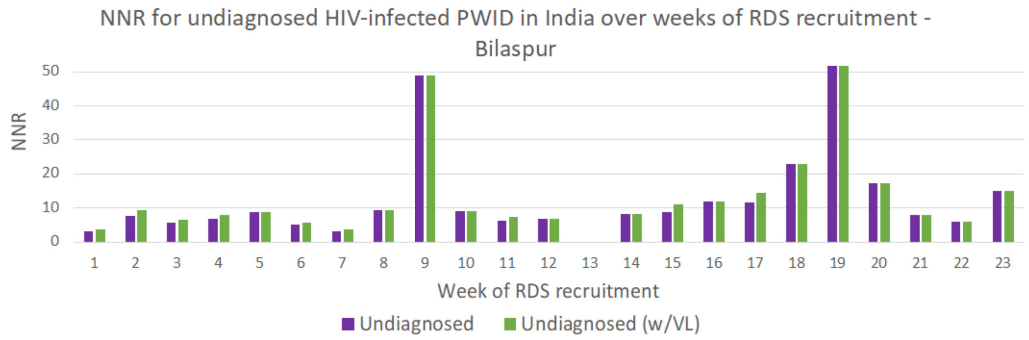
RDS: respondent-driven sampling
NNR: Average number of people who inject drugs (PWID) recruited/screened in order to identify one undiagnosed HIV-infected PWID
Identification rate per week: Average number of undiagnosed PWIED identified per week

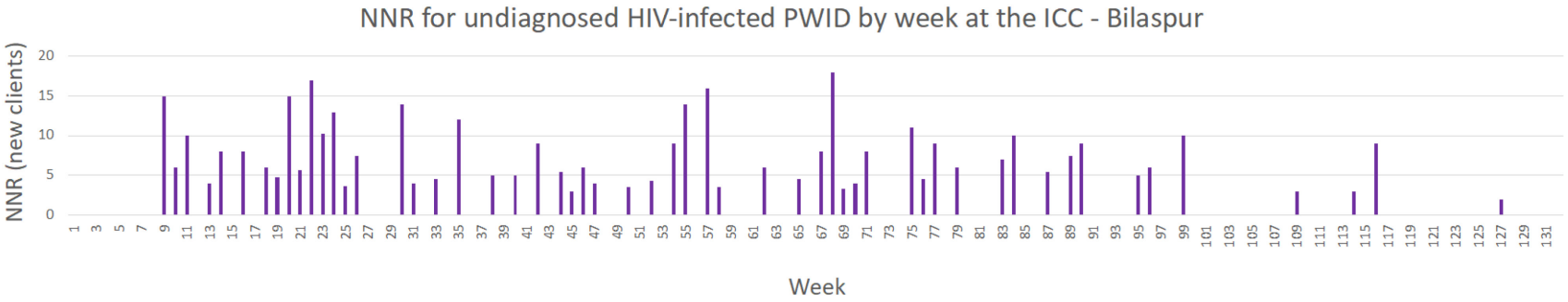
Supplementary Figures 2.1 NNR and number undiagnosed HIV-infected PWID per week for ICCs and RDS, stratified by city



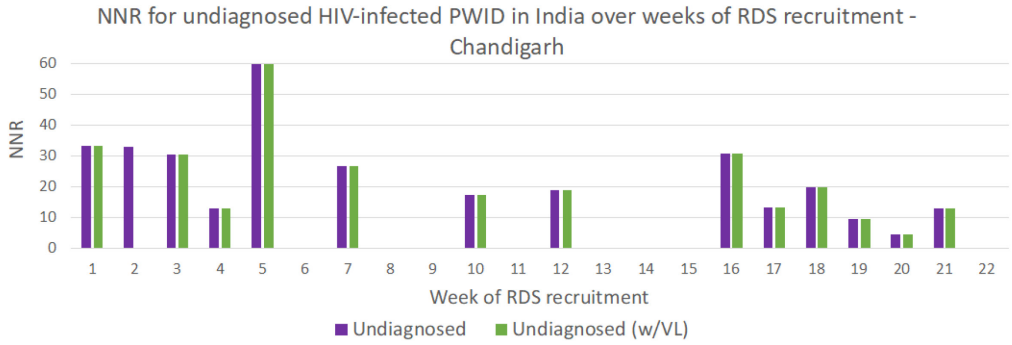


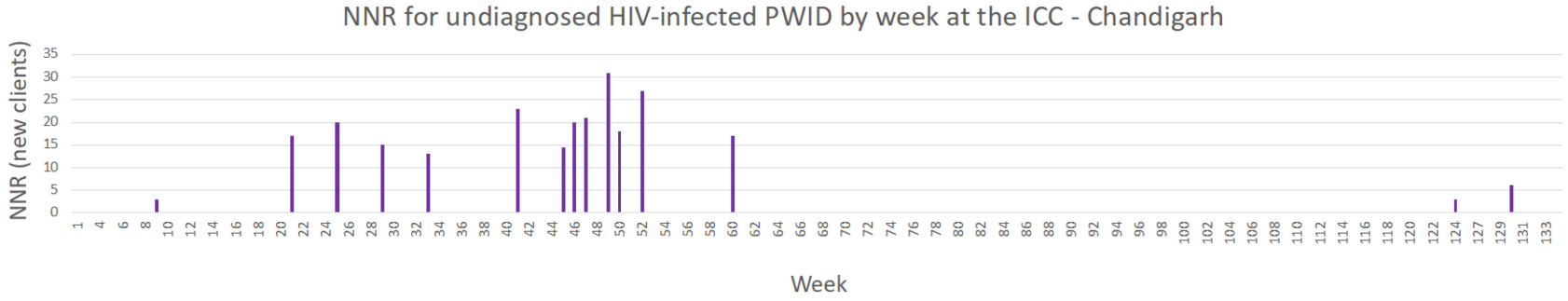
Weeks with no bar indicate no undiagnosed individuals were identified in that week, resulting in an undefined NNR



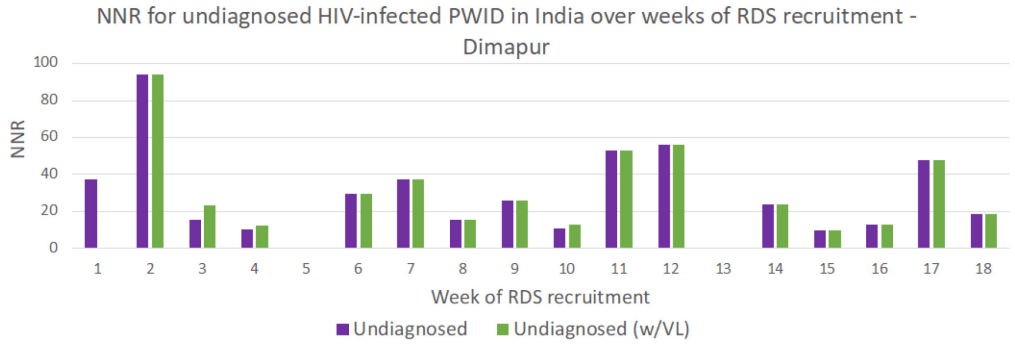


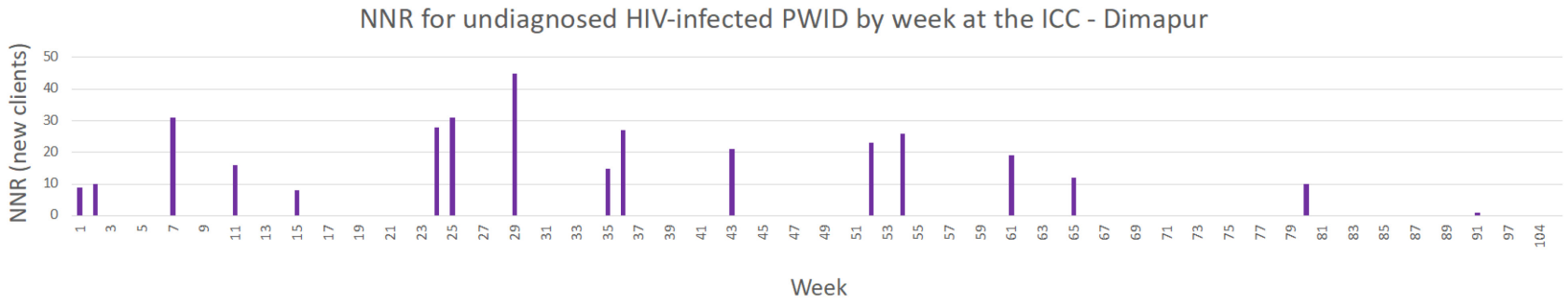
Weeks with no bar indicate no undiagnosed individuals were identified in that week, resulting in an undefined NNR



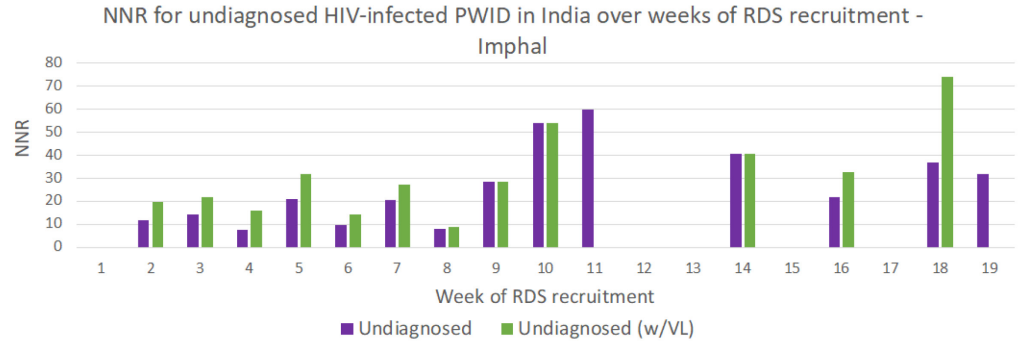


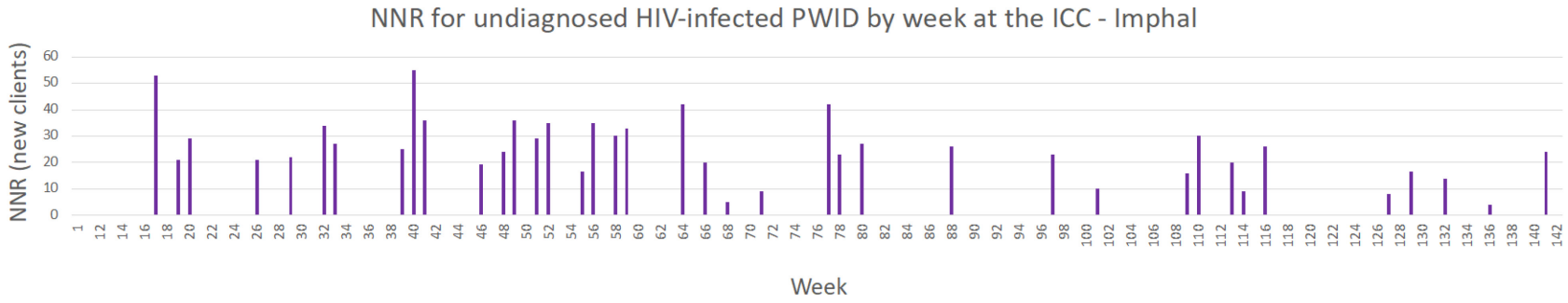
Weeks with no bar indicate no undiagnosed individuals were identified in that week, resulting in an undefined NNR



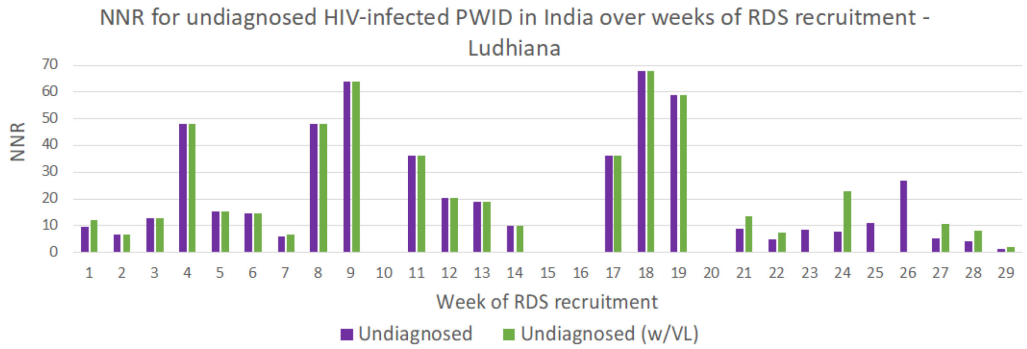


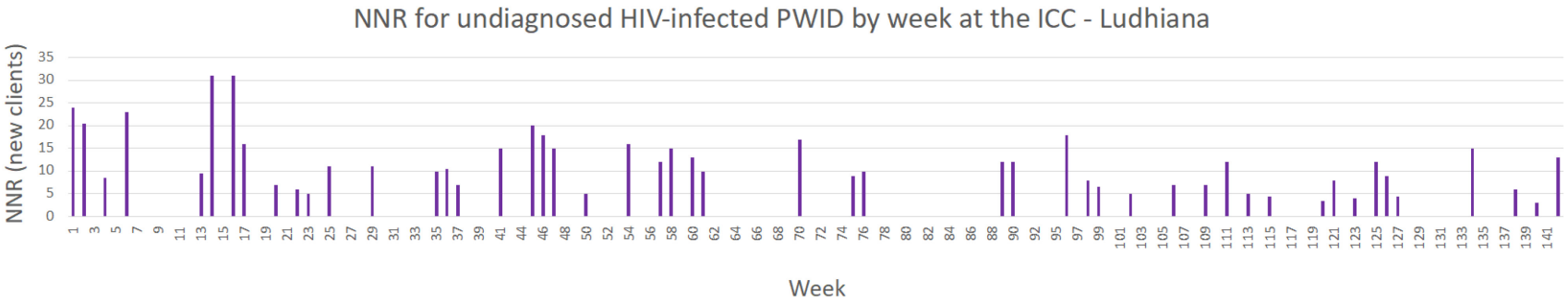
Weeks with no bar indicate no undiagnosed individuals were identified in that week, resulting in an undefined NNR



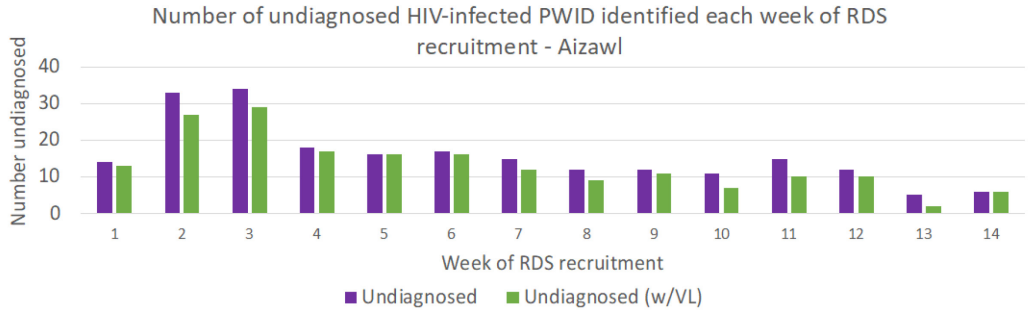


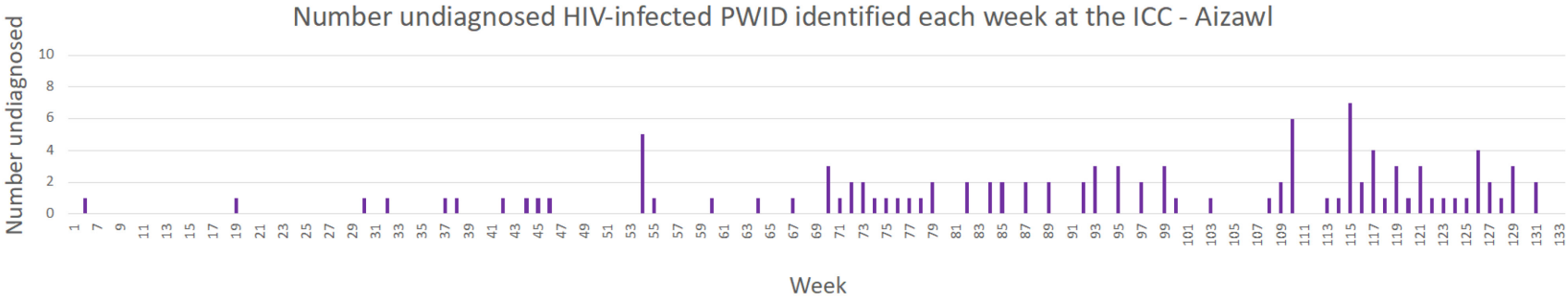
Weeks with no bar indicate no undiagnosed individuals were identified in that week, resulting in an undefined NNR

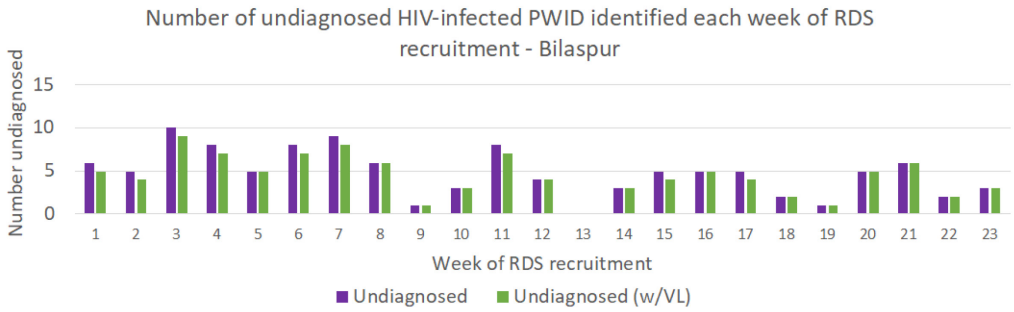


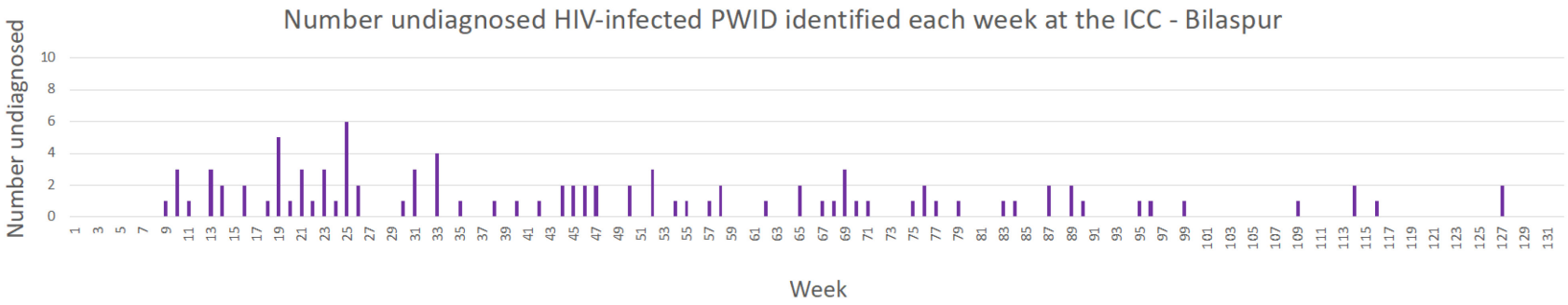


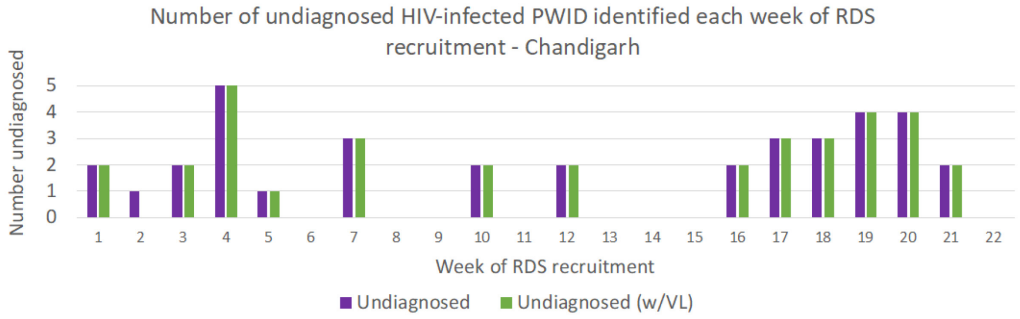
Weeks with no bar indicate no undiagnosed individuals were identified in that week, resulting in an undefined NNR

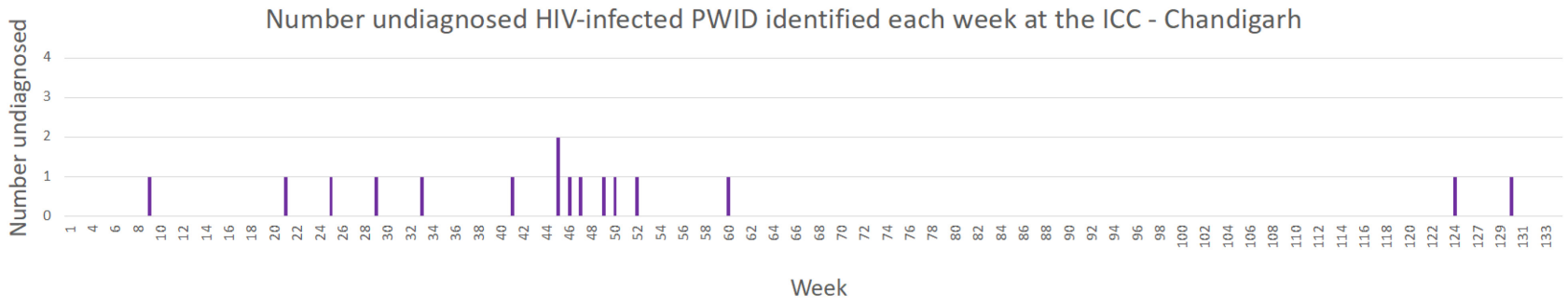

Number of undiagnosed HIV-infected PWID identified each week of RDS recruitment - Aizawl
Number undiagnosed
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Week of RDS recruitment
Undiagnosed
Undiagnosed (w/VL)

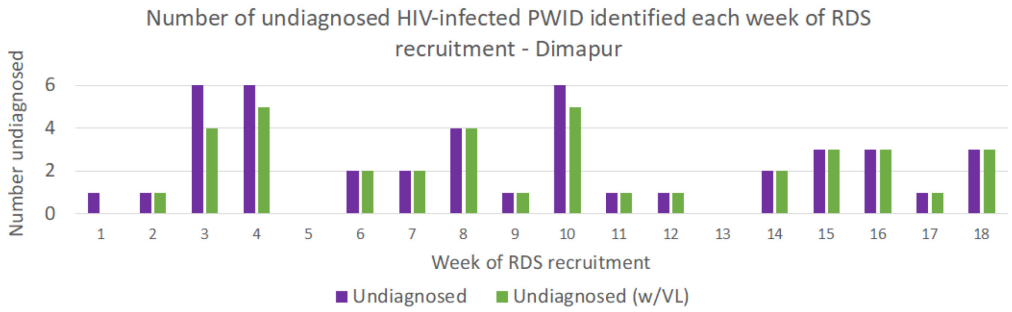

Number undiagnosed HIV-infected PWID identified each week at the ICC - Aizawl
Number undiagnosed
10
8
6
4
2
0
Week

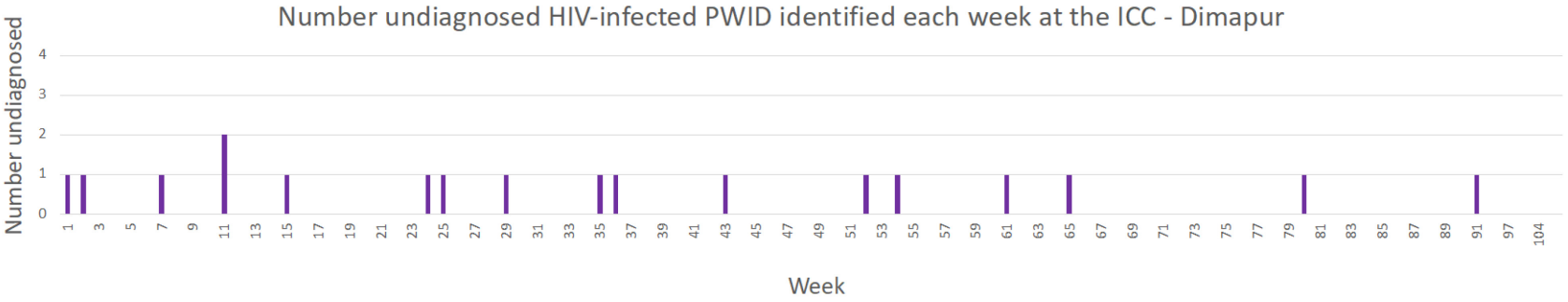

Number of undiagnosed HIV-infected PWID identified each week of RDS recruitment - Bilaspur
Number undiagnosed
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
Week of RDS recruitment
Undiagnosed
Undiagnosed (w/VL)

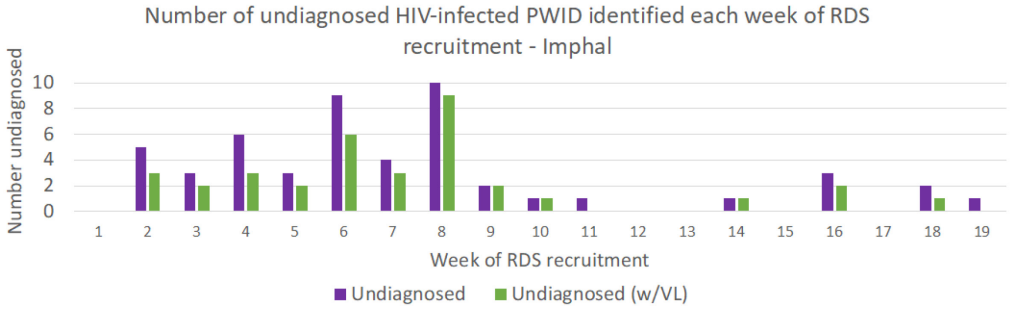

Number undiagnosed HIV-infected PWID identified each week at the ICC - Bilaspur
Number undiagnosed
10
8
6
4
2
0
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65 67 69 71 73 75 77 79 81 83 85 87 89 91 93 95 97 99 101 103 105 107 109 111 113 115 117 119 121 123 125 127 129 131
Week

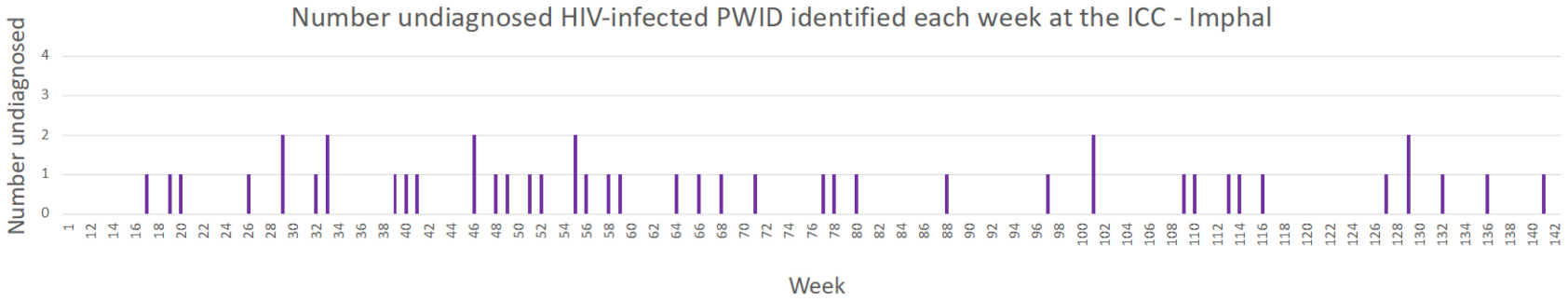

Number of undiagnosed HIV-infected PWID identified each week of RDS recruitment - Chandigarh
Number undiagnosed
0
1
2
3
4
5
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Week of RDS recruitment
Undiagnosed
Undiagnosed (w/VL)

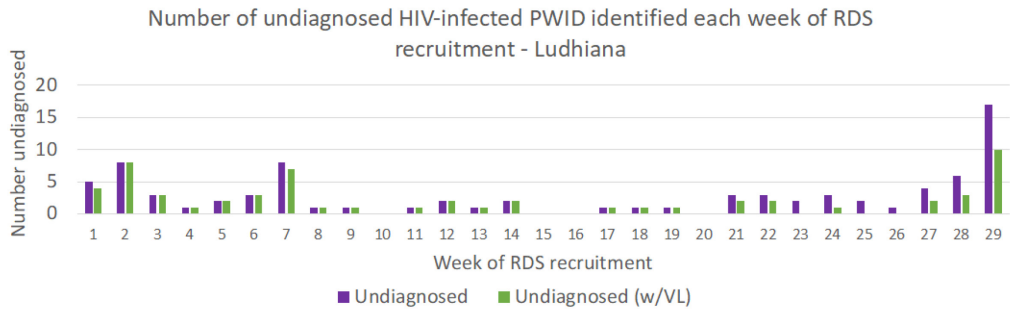

Number undiagnosed HIV-infected PWID identified each week at the ICC - Chandigarh
Number undiagnosed
0
1
2
3
4
1 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62 64 66 68 70 72 74 76 78 80 82 84 86 88 90 92 94 96 98 100 102 104 106 108 110 112 114 116 118 120 122 124 127 129 131 133
Week

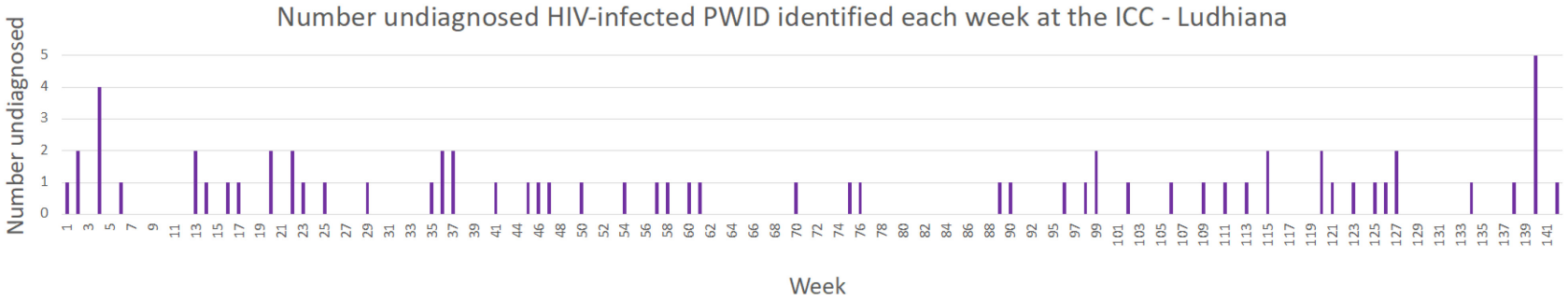

Number of undiagnosed HIV-infected PWID identified each week of RDS recruitment - Dimapur
Number undiagnosed
0
2
4
6
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Week of RDS recruitment
Undiagnosed
Undiagnosed (w/VL)


Number undiagnosed HIV-infected PWID identified each week at the ICC - Dimapur
Number undiagnosed
0
1
2
3
4
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65 67 69 71 73 75 77 79 81 83 85 87 89 91 97 104
Week


Number of undiagnosed HIV-infected PWID identified each week of RDS recruitment - Imphal
Number undiagnosed
0
2
4
6
8
10
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Week of RDS recruitment
Undiagnosed
Undiagnosed (w/VL)


Number undiagnosed HIV-infected PWID identified each week at the ICC - Imphal
Number undiagnosed
0
1
2
3
4
Week


Number of undiagnosed HIV-infected PWID identified each week of RDS recruitment - Ludhiana
Number undiagnosed
20
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Week of RDS recruitment
Undiagnosed
Undiagnosed (w/VL)


Number undiagnosed HIV-infected PWID identified each week at the ICC - Ludhiana
Number undiagnosed
5
4
3
2
1
0
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 44 46 48 50 52 54 56 58 60 62 64 66 68 70 72 74 76 78 80 82 84 86 88 90 92 95 97 99 101 103 105 107 109 111 113 115 117 119 121 123 125 127 129 131 133 135 137 139 141
Week

Chapter 3: Predicting identification of undiagnosed HIV-infected people who inject drugs in India using respondent-driven sampling

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ABSTRACT

Background Novel strategies are needed to reach the UNAIDS 90-90-90 target, especially for PWID and other key populations. Respondent-driven sampling (RDS) is a rapid, effective method for reaching PWID. The objective of this analysis was to explore easy-to-collect characteristics of PWID associated with recruiting undiagnosed or viremic people who inject drugs living with HIV (PLWH) into an RDS sample and identify in which settings these characteristics predict recruitment best.

Methods In 2013, a cross-sectional sample of 14,481 PWID across 15 Indian cities (~1000/city) was accrued using RDS, initiated by two seeds; all participants were given 2 coupons to recruit other PWID. Participants underwent a blood draw, HIV testing, and completed a survey. Undiagnosed PLWH were individuals who tested positive and denied a prior diagnosis; viremic PLWH were individuals with a detectable HIV viral load. We evaluated predictive accuracy of recruiter characteristics in recruitment of undiagnosed/viremic PLWH using the area under the receiver operator curve (AUROC) from logistic regression models and a final multivariable model was applied to bootstrapped samples of each city to examine predictive ability in different types of settings.

Results Median age was 30, most were men (94%), and 20% were HIV-infected, of whom 58% were previously undiagnosed; 10% and 13% of participants recruited an undiagnosed and viremic PLWH, respectively. HIV and HCV infection along with factors associated with higher HIV risk (e.g., sharing needles/syringes, large network size) were most strongly associated with recruiting an undiagnosed/viremic PLWH. Among PWID with HIV/HCV co-infection, a large

network size (≥51), and that reported sharing needles/syringes in the prior 6 months, 25% recruited at least one undiagnosed PLWH and 34% recruited a viremic PLWH. A multivariable model with 10 characteristics predicted with moderate ability the recruitment of an undiagnosed (AUROC=0.67) and viremic (0.66) PLWH. The model performed best in areas with low harm reduction access and for recruitment of an undiagnosed PLWH, prediction was best in settings with low HIV/HCV services and high HIV incidence.

Conclusions Recruitment patterns suggest PWID with HIV/HCV infection, who are central in their network, and engage in risky behaviors are more likely to recruit PWID with undiagnosed/viremic HIV. These easily obtainable characteristics could be used to target an RDS in order to identify undiagnosed/viremic PLWH more efficiently.

INTRODUCTION

In 2014, UNAIDS set an ambitious target to end the HIV epidemic by 2020, which we are rapidly approaching. The target aims for 90% of all those living with HIV to be diagnosed, 90% of those diagnosed to be on sustained antiretroviral therapy (ART), and 90% of those on ART to have undetectable viral load[1]. Importantly, these must be approached with principles of human rights and inclusion of all those living with HIV, especially key populations (e.g., men who have sex with men [MSM], people who inject drugs [PWID], transgender individuals, sex workers) who experience stigma, discrimination, and marginalization, continue to have a disproportionate burden of HIV[2], and often lag behind the general population in the HIV care continuum and 90-90-90-target[3]. In many areas of the world, HIV epidemics are growing due to injection drug use; PWID account for an estimated 30% of new infections outside sub-Saharan Africa[4].

Respondent-driven sampling (RDS), a type of chain referral sampling, is now widely used in HIV research and surveillance, especially in key populations such as MSM, PWID, and female sex workers[5,6]. These populations do not have known sampling frames from which to sample and can be more difficult to reach due to stigma and criminalization. RDS is able to overcome these barriers by leveraging individuals' social networks for direct recruitment of study participants from the target population itself, rather than being driven by study staff. Given a set of assumptions, estimates can be weighted to produce unbiased population characteristics of the underlying target population[7], such as HIV prevalence or risk behaviors, which is most often the goal of the research - to characterize the epidemic and risk factors in a particular population to guide public health funding and programs.

Among PWID from 15 cities across India in 2013, we previously found that the largest drop in the HIV care continuum was at diagnosis with only approximately 40% of those HIV-infected being aware of their status[8] - well below the UNAIDS target of 90%. Quickly identifying persons living with HIV who are undiagnosed or not on ART is vital, not only for their individual health and well-being, but because they are likely to have high viral loads and thus able to efficiently transmit HIV to others such as their sexual or injecting partners. In our prior work, we found RDS to be a rapid, effective method for reaching PWID and MSM in India, especially those who are HIV-infected but undiagnosed or viremic[9]. Other researchers have similarly observed that among MSM in sub-Saharan Africa, HIV-infected study participants recruited in later waves of an RDS (i.e., deeper in the network) were less likely to be aware of their status[10,11]. Therefore, not only is RDS an efficient way to reach these key populations in general but RDS may specifically help to identify individuals within these populations that may be even more difficult to reach, less likely to self-refer to services, and/or be unaware of their HIV risk. These data collectively support the use of RDS as a strategy to reach people at high-risk for HIV and that are not currently engaging in HIV-related services. Such strategies are especially important given the UNAIDS 90-90-90 target.

Since RDS rapidly reached a large number of PWID, especially those that were not engaged in HIV-related services, it is of interest to understand whether it might be possible to steer RDS to increase the efficiency of identifying undiagnosed or viremic PWID living with HIV (PLWH). The objective of this analysis was to explore easy-to-collect characteristics of PWID associated with recruiting undiagnosed or viremic PLWH into an RDS sample and to identify in which settings these characteristics predict recruitment best.

METHODS

Study design

Data used for this analysis were collected as part of a cluster-randomized trial, the National Collaboration on AIDS (NCA) trial (ClinicalTrials.gov identifier: NCT01686750) among MSM and PWID in India[12]. This analysis is restricted to the cross-sectional baseline assessment data of the PWID stratum.

Participants were recruited using RDS from 15 different Indian cities (Table 3.1), representing different regions and stages of the HIV epidemic (i.e., both established epidemics and emerging epidemics), between January and December 2013. Approximately 1000 PWID were recruited in each city, with the exception of Moreh, where recruitment was stopped early due to civil unrest in the area. The RDS was initiated in each city using 2 seeds (3 in Gangtok); seeds are PWID that are well-connected and influential in their community. Each seed and subsequent study participant were given two recruitment coupons to distribute to others that they know inject drugs in the city. Coupons were bar-coded with identification numbers to link recruiters and their recruits and included a hologram to prevent duplication of coupons. Individuals that received a coupon, voluntarily visited the study center, and if eligible, were enrolled, completed study procedures, and received 2 recruitment coupons to distribute to their network at random. Recruitment continued until the desired sample size in each city was met (1000). Eligibility criteria to enroll in the study included (1) being at least 18 years old, (2) provision of informed consent, (3) possession of a valid coupon unless a seed, and (4) self-reported injection drug use in the prior 24 months. Dual incentives were provided for study participation and recruitment.

Study participants received INR 250 (US $3.8) for completing study procedures and INR 50 (US $0.80) for each eligible study participant they recruited into the study.

Study procedures

Following consent, study participants provided a blood sample and completed an interviewer-administered questionnaire that collected information on socio-demographics, HIV and HCV testing and care history, injection and sexual risk behaviors, harm reduction, and network characteristics. HIV pre- and post-test counseling in addition to appropriate referrals to care for HIV-infected participants were provided with rapid HIV testing. HIV testing was conducted in accordance with Indian guidelines using 3 rapid tests: Alere Deterimine 1/2 (Alere Medical, Chiba, Japan), First Response HIV Card Test 1-2.0 (Premier Medical Corporation, Daman, India), and Signal Flow Through HIV 1+2 Spot/Immunodot Test Kit (Span Diagnostics, Surat, India). Using stored blood samples, HCV antibody testing was conducted using Genedia HCV ELISA 3.0 (Green Cross Medical Science, Chungbuk, Korea) and HIV-1 RNA (viral load) quantification was conducted for all HIV-infected participants using Abbott RealTime HCV assay (Abbott Laboratories, Abbott Park, Illinois, US).

Statistical methods

The main outcome of interest is recruitment of at least one undiagnosed PWID living with HIV (PLWH) via the RDS. A participant was defined as undiagnosed if they had a positive HIV test at the study visit and denied a prior diagnosis on the questionnaire. Identification codes on the recruitment coupons allowed for the linkage of recruiter and their recruits in the data. If a study participant recruited no one or only HIV negative study participants or PLWH that were

diagnosed prior to the study, they were considered not to have the outcome of interest. There were a number of participants (n=251) who were HIV-infected and did not report a prior diagnosis but had an undetectable viral load (<150 copies/mL). These participants were categorized as previously diagnosed, since they were likely on antiretroviral therapy (confirmed via a sub-study on ART levels in blood samples). As a secondary analysis, we examined an objective outcome, namely recruitment of at least one viremic (HIV viral load ≥150 copies/mL) PLWH, regardless of self-reported diagnosis status.

Exploratory data analysis included the frequency/percentage and median/interquartile range (IQR) of characteristics by outcome status - recruiting/not recruiting an undiagnosed/viremic PLWH. The percentages and medians/IQRs are unweighted as the focus of this analysis is the pattern of RDS recruitment, not any inference to the underlying target population. Correlates of recruiting an undiagnosed/viremic PLWH were explored using logistic regression models. Correlates selected for investigation were easy-to-collect and broadly characterize the PWID population and their HIV risk; they include self-reported socio-demographics (age, gender, marital status, education), injection risk behaviors (injection duration and sharing needles/syringes), harm reduction services utilization (needle/syringe exchange program [NEP] and opioid agonist therapy [OAT]), PWID network size (categorized using quartiles) and HIV and HCV status. Logistic regression models used a complete case analysis, dropping any observation with a missing correlate. Missingness was minimal with no more than 0.4% missing for any correlate: gender and marital status (n=1), HIV status (n=1), HCV status (n=2), and injection duration (n=57). The predictive accuracy of each correlate was assessed using the area under the receiver operator curve (AUROC) from the logistic regression.

Multivariable logistic models using all 15 cities were constructed including different combinations of characteristics. The overall predictive accuracy of the models was assessed using the AUROC. AUROCs of each model were statistically compared to identify the most parsimonious and predictive multivariable model (i.e., the final multivariable model). Additionally, for combinations of specific characteristics (e.g., HIV/HCV co-infected and with a large network size), recruitment efficiency was calculated which is the percent of individuals with the specific characteristic combination that recruited an undiagnosed/viremic PLWH.

To examine in which type of setting the final multivariable model best predicts recruiting an undiagnosed/viremic PLWH, we applied the multivariable model coefficients to 1000 bootstrapped samples of each city. First, separately for each city, participants were sampled with replacement from the third wave of recruitment. For any wave three participant that was sampled, all their descendants were included. Coefficients from the multivariable model were applied to this bootstrapped sample and the AUROC calculated. This process was repeated 1000 times for each city. The median and 2.5% and 97.5% percentile of the 1000 AUROCs were the AUROC point estimate and 95% confidence interval, respectively, for that city. In one or more of the bootstrapped samples for Gangtok and Moreh, no individuals had the outcome of interest (due to a low prevalence of the outcome in Gangtok and a high level of clustering of the outcome by recruitment chain in Moreh) and thus the AUROC could not be calculated for these two sites. Next, we calculated city-level characteristics including socio-demographics, HIV/HCV prevalence, annual HIV incidence, HIV care continuum outcomes, prevalence of HIV viremia (percent of total population with HIV viral load ≥150 copies/mL), HCV testing and awareness,

harm reduction services utilization, and injection drug use risk behaviors. City-level characteristics were calculated incorporating RDS-II weights[13] so that the characteristics are reflective of the underlying target population, with the exception of cross-sectional annual HIV incidence, which is unweighted and calculated using a validated multi-assay algorithm[14]. A Spearman rank correlation (ρ) was used to assess the relationship between the AUROC calculated from each of the city bootstrapped models and city-level characteristics. For moderate to strong correlations ($\rho \geq |0.3|$), we further examined the relationship using a scatterplot of the AUROC and city-level characteristic with a linear prediction.

Analyses were conducted using Stata (StataCorp. 2017. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC). P-values were considered statistically significant at <0.05.

Ethical clearances

This study was approved by the institutional review boards of the Johns Hopkins University School of Medicine and the Y.R. Gaitonde Centre for AIDS Research and Education.

RESULTS

A total of 14,481 PWID were enrolled of whom 2,915 were HIV-infected (20%); 58% of PLWH were unaware of their infection. Median age was 30 years (IQR: 24 - 36), 6% were women, and 90% were actively injecting drugs in the prior six months. Overall, 43% of participants did not recruit anyone, 14% recruited one PWID, and 43% recruited two PWID.

Recruiting undiagnosed PLWH

Approximately 9% (n=1286) of study participants recruited at least one undiagnosed PLWH. In univariable analysis, those that recruited an undiagnosed PLWH were significantly older (odds ratio [OR] per 10 year increase: 1.13, confidence interval [CI]: 1.06 - 1.21), more likely to be HIV and/or HCV-infected (HIV mono-infected OR: 1.69, 95% CI: 1.30 - 2.20; HCV mono-infected OR: 2.36, 95% CI: 2.05 - 2.71; HIV/HCV co-infected OR: 3.60, 95% CI: 3.10- 4.18, all vs. HIV/HCV negative,), report recently sharing a needle/syringe (OR: 1.40, 95% CI: 1.24 - 1.57), recently use a NEP (OR: 1.30, 95% CI: 1.16 - 1.46), and have a large PWID network (OR ≥51 vs. ≤8: 1.74, 95% CI: 1.46 - 2.07) (**Table 3.1**). Women (OR vs. men: 0.67, 95% CI: 0.50 - 0.89), those married or living with their partner (OR vs. never married: 0.86, 95% CI: 0.76 - 0.97), and those with a higher education (OR at least high school vs. no/primary school: 0.62, 0.52 -0.73) were less likely to recruit an undiagnosed PLWH. The independent predictive accuracy of the characteristics was lowest for recently using OAT (AUROC=0.50), injection duration (0.51), and gender (0.51). Predictive accuracy was highest for HIV/HCV status (AUROC=0.64) and city (0.71).

The predictive ability of different multivariable models for recruiting an undiagnosed PLWH are presented in **Table 3.2.** Model 5 with demographics, HIV/HCV infection status, network size, injection duration, needle/syringe sharing, and harm reduction had the highest AUROC (0.67; 95% CI: 0.65 - 0.68) and was significantly higher than all other models. However, the predictive ability of the model with only HIV/HCV infection status and network size was also fairly high (AUROC=0.64); addition of recently sharing a needle/syringe to this model did not significantly improve prediction. Compared to univariable analysis, associations tended to be similar in the

final multivariable analysis using model 5 (**Table 3.1**); recent NEP use was no longer significantly associated (OR: 1.09, 95% CI: 0.97 - 1.24) and injection duration became significantly negatively associated (OR by 5-year increase: 0.86, 95% CI: 0.82 - 0.91) after adjustment. Recruitment efficiency (**Table 3.2)** was highest among those with HIV/HCV co-infection, a network size ≥51, and that recently shared a needle/syringe (24.7%). Second highest efficiency was among those with HIV/HCV co-infection and a network size ≥51 (18.8%).

The AUROCs for each city using the bootstrap approach are presented in **Table 3.3** along with city-level characteristics; AUROCs ranged from 0.66 to 0.50. Predictive ability was poorest in Bhubaneshwar (AUROC=0.50) and Aizawl (0.52). The Spearman rank correlation of the AUROC for each city and its city-level characteristics are presented in **Figure 3.1**. Using a cut-off of |0.3| to indicate a moderate to strong correlation (shaded area of **Figure 3.1**), annual HIV incidence (ρ=0.54) was positively correlated with predictive ability. The percentage of PLWH satisfying steps in the HIV care continuum was negatively correlated with predictive ability, specifically, percentage aware of HIV positive status (ρ=-0.45), linked to HIV care (-0.48), antiretroviral therapy (ART) use among those eligible for treatment (-0.41), and undetectable HIV viral load among those ART eligible (-0.40). Percentage ever receiving an HCV test (ρ=-0.35), aware of HCV positive status (-0.32), recently using a NEP (ρ=-0.79), and recently using OAT (-0.51) were also negatively correlated with predictive ability. NEP use was the only correlation that was statistically significant. Scatterplots with linear predictions for these city-level characteristics and bootstrapped AUROCs are presented in **Figure 3.2a**.

Recruiting a viremic PLWH

Recruiting at least one viremic PLWH was marginally more common (n=1822, 12.6%) than recruiting an undiagnosed PLWH. Univariable associations and their AUROCs were comparable to recruiting an undiagnosed PLWH (**Supplementary Table 3.1**). Predictive ability of multivariable models for recruiting a viremic PLWH (**Table 3.2**) were also very similar to models recruiting an undiagnosed PLWH. Model 5 with demographics, HIV/HCV infection status, network size, injection duration, needle/syringe sharing, and harm reduction had the highest AUROC (0.66; 95% CI: 0.65 - 0.67) and was significantly higher than all other models; multivariable associations of characteristics were also similar to recruiting an undiagnosed PLWH (**Supplementary Table 3.1**). Efficiency also showed the same pattern; recruitment efficiency was highest among those with HIV/HCV co-infection, a network size ≥51, and who recently shared a needle/syringe (33.8%). Second highest efficiency was among those with HIV/HCV co-infection and a network size ≥51 (28.1%).

The AUROCs for each city using the bootstrap approach were slightly higher compared to recruiting an undiagnosed PLWH and the relative ability of the model to predict in each city differed from what was observed for undiagnosed PLWH (**Table 3.1**). AUROCs ranged from 0.77 to 0.55. Predictive ability was positively correlated with the percentage with at least a secondary school education (ρ=0.45) and the percentage female (0.42) (**Figure 3.1**). Similar to recruiting an undiagnosed PLWH, the percentage recently using a NEP (ρ=-0.43) and OAT (-0.38) were negatively correlated with predictive ability, though to a lesser extent. Scatterplots with linear predictions for these city-level characteristics and bootstrapped AUROCs are presented in **Figure 3.2b**. No HIV- or HCV-related city-level characteristics were moderately or

strongly correlated with predictive ability of recruiting a viremic PLWH and no correlations reached statistical significance.

DISCUSSION

Using easy-to-collect characteristics of PWID, we were able to predict which individuals are most likely to know and recruit an undiagnosed and viremic PLWH into an RDS. HIV and HCV infection along with factors associated with higher HIV risk were most strongly associated with recruiting an undiagnosed and viremic PLWH. Among PWID with HIV/HCV co-infection, a large network size, and that recently shared needles/syringes, a quarter recruited an undiagnosed PLWH and a third recruited a viremic PLWH. Together, a multivariable model with 10 characteristics including basic demographics, HIV/HCV status, injection drug use characteristics/behaviors, harm reduction service utilization, and network size was able to predict with moderate ability the recruitment of an undiagnosed and viremic PLWH. When this model was applied to different contexts across India, it performed best in areas with low harm reduction access. Additionally, specifically for recruitment of an undiagnosed PLWH, prediction was best in settings with low HIV/HCV services availability or accessibility in addition to areas with emerging or ongoing epidemics (i.e., high HIV incidence).

Similar to our findings, prior studies examining RDS recruitment patterns among PWID in Mexico and the United States found that HIV-infected RDS participants are more likely to recruit others that are HIV-infected[15,16]. Our findings go one step further to suggest that those HIV-infected - whether they are aware of their status or not - are more likely to know and recruit someone that is HIV-infected *but undiagnosed or viremic*. This assortativity or homophily

(similarity or preference for others with similar characteristics) within RDS recruitment chains by HIV status was expected as HIV infection tends to cluster within social or injecting networks, a result of direct transmission and/or similar high-risk behaviors (e.g., frequency of injecting, sharing of injection paraphernalia)[17,18]. We also found that prevalent HCV infection was associated with recruiting an undiagnosed and viremic PLWH, with those co-infected with HCV and HIV most strongly associated. It is possible that co-infected PWID are currently or were frequently engaging in high-risk behaviors and are therefore more likely to be socially connected to others with similar behaviors. Though one of the assumptions of RDS recruitment is random selection of individuals within a person's network[13], it is also possible that people are preferentially recruiting individuals based on certain characteristics as others have found[19-22]. Without data on the full sociometric network or in-depth questions on network characteristics, it is difficult to ascertain which scenario is the truth[23] - are HIV-infected PWID more likely to know someone that is HIV-infected but undiagnosed *or* are they choosing to recruit a network member that is engaging in more high-risk behaviors? The answer to this has implications for calculating population estimates using RDS data[24] but if using RDS as a strategy to identify individuals in order to engage them in HIV services, there need not be a distinction.

Our multivariable prediction model for recruiting an undiagnosed and viremic PLWH included only 10 covariates that would take 5 minutes or less to collect from PWID, with the exception of rapid tests for HIV and HCV, which would likely take about 20-30 minutes. Together, these characteristics were able to predict with fairly high ability given the rare outcomes - only 9% and 13% of the sample recruited an undiagnosed or viremic PLWH, respectively. However, results suggest that the predictive ability of the model varied by setting. For recruitment of both

undiagnosed and viremic PLWH, better predictive ability was seen in cities with lower utilization of NEP and OAT. For undiagnosed PLWH, the model also performed better in areas with high HIV incidence and in those that were doing worse in terms of the HIV care continuum, specifically low levels of diagnosis, linkage to care, antiretroviral therapy use, and undetectable viral load among positives. Similarly, predictive ability was better in cities where fewer PWID had ever been tested for HCV and fewer of HCV-infected PWID were aware of their status. This is somewhat intuitive since undiagnosed PLWH would be more prevalent and well-connected within PWID networks in settings in which there are higher numbers of new HIV infections but little access to basic harm reduction and HIV/HCV services compared to those in settings with successful harm reduction and HIV service programs for PWID. Therefore, our findings suggest that using a network-based approach similar to RDS in which recruitment is steered using these basic predictors in order to identify more undiagnosed PLWH would be most appropriate and effective for settings with growing HIV epidemics and low PWID-targeted and HIV service availability. Available information or data on a local epidemic could be used to determine the appropriateness of this approach or alternatively, an RDS could be run for at least six waves - when equilibrium of characteristics is generally reached[25] - to characterize the HIV epidemic, PWID harm reduction, and HIV/HCV service utilization.

Predictors were very similar for the two outcomes, recruitment of an undiagnosed PLWH and a viremic PLWH. Given the very low awareness of HIV-infected PWID, a large portion of the viremic population - more than two-thirds - are indeed undiagnosed, which may explain this finding. On the other hand, the settings in which the multivariable model performed best differed for the two. There is significant variability across the different Indian regions and cities

represented in our sample, especially in the availability and accessibility of HIV-related services and therefore HIV care continuum outcomes among PWID[8]. This results in different mixtures of undiagnosed individuals and viremic individuals within the population of people living with HIV, making the application of one model for recruiting a viremic PLWH across different contexts less helpful. However, the ultimate goal of any HIV program or intervention is to reduce the number of viremic individuals in the population in order to reduce transmission, as evidenced by the UNAIDS 90-90-90 target, treatment as prevention (TasP), and the recent U=U campaign[26]. Diagnosis is only the first step; there must also be continued strong support for people living with HIV through all stages of care including access and adherence to effective therapy.

There are several limitations to this work. Awareness of HIV status, as well as most of the predictors, were self-reported using the interviewer-administered questionnaire which is subject to biases such as recall and social desirability bias. Trained interviewers were used to mitigate these biases. To partially address this issue for our main outcome, we were able to identify and re-classify HIV-infected individuals that did not report a prior diagnosis but were likely to already be aware of their status because of an undetectable viral load. While the sample size for the individual-level analyses was quite large (>14,000), the correlation analysis to explore in which settings our prediction model performed best was at the city-level thus only had a sample size of 13 and 14. This limited our statistical power to identify which city-level characteristics were significantly associated with predictive ability. City-level characteristics were calculated using the RDS-II estimator[13] which should provide an unbiased estimate of the underlying target

population but we are unable to verify that these RDS-weighted estimates are reflective of our target population (i.e., PWID in each city).

These results add to our prior work highlighting the rapid identification of key populations in India using RDS[9] by also showing that recruitment has identifiable patterns. This suggests the potential to leverage RDS in order to efficiently identify the large fraction of those PWID that are HIV-infected but unaware of their infection and viremic, thus working towards the 90-90-90 UNAIDS target and ultimately, decreasing transmission and incidence.

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Table 3.1 Characteristics of recruiting an undiagnosed PLWH and their predictive accuracy

Characteristic	**Did not recruit undiagnosed PLWH (N=13195)**	**Recruited undiagnosed PLWH (N=1286)**						
	n (row %)/ median (IQR)	n (row %)/ median (IQR)	**Odds Ratio**	**95% CI**	**AUROC**	**95% CI**	**Adjusted Odds Ratio‡**	**95% CI**
City								
Northeast region								
Aizawl	927 (92.5)	75 (7.5)	Reference					
Churachandpur	908 (90.6)	94 (9.4)	1.28	0.93 - 1.76				
Dimapur	967 (96.5)	35 (3.5)	0.45	0.30 - 0.67				
Gangtok	1001 (99.8)	2 (0.2)	0.02	0.01 - 0.10				
Imphal	8991 (88.9)	111 (11.1)	1.54	1.13 - 2.09				
Lunglei	984 (98.2)	18 (1.8)	0.23	0.13 - 0.38				
Moreh	389 (84.8)	70 (15.3)	2.22	1.57 - 3.15				
North region								
Amritsar	887 (88.6)	114 (11.4)	1.59	1.17 - 2.16	0.711	0.698 - 0.725	--	
Chandigarh	911 (91.3)	87 (8.7)	1.18	0.86 - 1.63				
New Delhi	879 (87.8)	122 (12.2)	1.72	1.27 - 2.32				
Ludhiana	868 (86.6)	134 (13.4)	1.91	1.41 - 2.57				
Central region								
Bhubaneshwar	989 (98.7)	13 (1.3)	0.16	0.09 - 0.29				
Bilaspur	896 (89.4)	106 (10.6)	1.46	1.07 - 1.99				
Kanpur	740 (73.9)	262 (26.2)	4.38	3.33 - 5.76				
Mumbai	958 (95.7)	43 (4.3)	0.55	0.38 - 0.82				
Age, years (model by 10 years)	29 (24-36)	30 (25-37)	1.13	1.06 - 1.21	0.537	0.520 - 0.553	1.28	1.17 - 1.39
Gender								
Man	12404 (91.0)	1234 (9.0)	Reference				Reference	
Woman	783 (93.8)	52 (6.2)	0.67	0.50 - 0.89	0.510	0.504 - 0.515	0.59	0.43 - 0.80
Transgender/*Hijra*	7 (100)	0 (0)	*	*			*	*
Marital status								

Characteristic	Did not recruit undiagnosed PLWH (N=13195)	Recruited undiagnosed PLWH (N=1286)						
	n (row %)/ median (IQR)	n (row %)/ median (IQR)	Odds Ratio	95% CI	AUROC	95% CI	Adjusted Odds Ratio‡	95% CI
Never married	5477 (90.6)	568 (9.4)	Reference				Reference	
Married/long-term or living w/partner	6124 (91.8)	545 (8.2)	0.86	0.76 - 0.97	0.521	0.506 - 0.536	0.81	0.71 - 0.93
Widowed/divorced/ separated	1593 (90.2)	173 (9.8)	1.05	0.88 - 1.25			0.86	0.71 - 1.04
Education								
No/primary school	4475 (89.0)	551 (11.0)	Reference				Reference	
Secondary school	6101 (91.9)	536 (8.1)	0.71	0.63 - 0.81	0.550	0.535 - 0.565	0.75	0.66 - 0.85
At least high school graduate	2618 (92.9)	199 (7.1)	0.62	0.52 - 0.73			0.69	0.58 - 0.82
HIV status								
Negative	10694 (92.6)	859 (7.4)	Reference					
Positive	2488 (85.4)	427 (14.7)	2.14	1.89 - 2.42	0.572	0.558 - 0.585	--	
Indeterminate	12 (100)	0 (0)	*	*				
HCV status								
Negative	8187 (94.3)	494 (5.7)	Reference		0.618	0.604 - 0.632	--	
Positive	5005 (86.3)	792 (13.7)	2.62	2.33 - 2.95				
HIV/HCV status								
HIV and HCV negative	7437 (94.6)	422 (5.4)	Reference				Reference	
HIV positive/HCV negative	750 (91.2)	72 (8.8)	1.69	1.30 - 2.20	0.637	0.621 - 0.652	1.89	1.44 - 2.48
HIV negative/HCV positive	3267 (88.2)	437 (11.8)	2.36	2.05 - 2.71			2.21	1.91 - 2.56
HIV and HCV positive	1738 (83.0)	355 (17.0)	3.60	3.10 - 4.18			3.36	2.86 - 3.94
Injection duration, years (model by 5 years)	6 (3-12)	7 (3-12)	1.01	0.97 - 1.05	0.508	0.491 - 0.524	0.86	0.82 - 0.91
Shared needle/syringe in past 6 months								
No	8786 (92.1)	756 (7.9)	Reference		0.539	0.525 - 0.553	Reference	
Yes	4490 (89.3)	530 (10.7)	1.40	1.24 - 1.57			1.17	1.44 - 1.32

Characteristic	Did not recruit undiagnosed PLWH (N=13195)	Recruited undiagnosed PLWH (N=1286)						
	n (row %)/ median (IQR)	n (row %)/ median (IQR)	Odds Ratio	95% CI	AUROC	95% CI	Adjusted Odds Ratio‡	95% CI
Needle/syringe exchange program use in past 6 months								
No	8580 (91.9)	757 (8.1)	Reference		0.531	0.517 - 0.545	Reference	
Yes	4615 (89.7)	529 (10.3)	1.30	1.16 - 1.46			1.09	0.97 - 1.24
Opioid agonist therapy in past 6 months								
No	11091 (91.2)	1077 (8.9)	Reference		0.502	0.491 - 0.512	Reference	
Yes	2104 (91.0)	209 (9.0)	1.02	0.88 - 1.19			0.89	0.76 - 1.05
PWID network size†								
≤8	3491 (93.6)	239 (6.4)	Reference		0.550	0.535 - 0.566	Reference	
9 to 20	3773 (90.9)	380 (9.2)	1.47	1.24 - 1.74			1.32	1.11 - 1.56
21 to 50	3181 (90.3)	340 (9.7)	1.56	1.31 - 1.85			1.34	1.12 - 1.60
≥51	2750 (89.4)	327 (10.6)	1.74	1.46 - 2.07			1.43	1.19 - 1.72

PLWH: person who injects drugs living with HIV; IQR: interquartile range; CI: confidence interval; AUROC: area under the receiver operator curve; HCV: Hepatitis C virus; PWID: person who injects drugs

‡Adjusted for all other covariates listed below; *Predicted the outcome perfectly and was thus dropped from the regression model; †Number of PWID they personally know in their city, categorized by quartile

Table 3.2 Predictive accuracy of multivariable models of recruiting an undiagnosed/viremic PLWH and recruitment efficiency of specific characteristics

Model No.	Characteristics	AUROC (95% CI)		Specific characteristics	Efficiency	
		Recruited undiagnosed PLWH	Recruited viremic PLWH		Recruited undiagnosed PLWH	Recruited viremic PLWH
1	Age, gender, marital status, education (demographics)	0.575 (0.558 - 0.591)	0.563 (0.549 - 0.577)	Age ≥30, male, never married, and no/primary education	15.1%	19.1%
2	HIV/HCV infection status and network size	0.643 (0.627-0.659)	0.649 (0.636 - 0.663)	HIV/HCV co-infected and network size ≥51	18.8%	28.1%
3	HIV/HCV infection status, network size, and recent needle/syringe sharing	0.644 (0.638 - 0.660)	0.649 (0.636 - 0.663)	HIV/HCV co-infected, network size ≥51, and recently shared needle/syringe	24.7%	33.8%
4	Recent needle/syringe sharing, NEP, OAT	0.559 (0.543 - 0.574)	0.559 (0.546 - 0.573)	Recently shared needle/syringe, used NEP, did not use OAT	10.7%	15.0%
5	Demographics, HIV/HCV infection status, network size, injection duration, recent needle sharing, NEP, OAT	0.666 (0.651 - 0.682)	0.661 (0.647 - 0.674)	Age ≥30, male, never married, no/primary education, HIV/HCV co-infected, network size ≥51, injecting for ≥5 years, recently shared needle/syringe, used NEP, and did not use OAT.	9.1%	18.2%

PLWH: people who inject drugs living with HIV; AUROC: area under the receiver operator curve from logistic regression model; NEP: needle/syringe exchange program; OAT: opioid agonist therapy

Table 3.3 Bootstrapped multivariable prediction of recruiting an undiagnosed/viremic PLWH by city and city-level characteristics

	Northeast Region							North Region				Central Region			
AUROC by city	**AZ**	**CR**	**DM**	**GT**	**IM**	**LG**	**MO**	**AM**	**CD**	**DL**	**LD**	**BE**	**BI**	**KA**	**MU**
Recruiting undiagnosed PLWH	0.522	0.592	0.605	*	0.579	0.555	*	0.602	0.583	0.542	0.547	0.500	0.664	0.607	0.543
95% CI	0.433 - 0.590	0.545 - 0.643	0.465 - 0.715	*	0.528 - 0.655	0.431 - 0.674	*	0.546 - 0.640	0.409 - 0.635	0.420 - 0.617	0.463 - 0.584	0.305 - 0.739	0.583 - 0.757	0.551 - 0.638	0.388 - 0.632
Recruiting viremic PLWH	0.563	0.617	0.576	0.769	0.624	0.620	*	0.618	0.584	0.548	0.544	0.546	0.654	0.613	0.602
95% CI	0.524 - 0.619	0.571 - 0.682	0.397 - 0.648	0.640 - 0.862	0.558 - 0.685	0.552 - 0.659	*	0.582 - 0.660	0.414 - 0.600	0.464 - 0.604	0.402 - 0.588	0.347 - 0.710	0.599 - 0.748	0.550 - 0.645	0.506 - 0.670
City-level characteristics (%)[1]															
Median age (years)	27.7	30.3	30.5	28.9	34.5	25.1	33.2	28.6	30.7	32.6	29.4	32.8	28.7	34.6	33.1
Female	18.7	22.7	14.1	6.7	12.3	12.1	23.2	1.2	0.4	0.0	0.2	0.1	0.5	0.7	3.5
At least secondary school education	93.8	73.4	66.5	82.7	71.1	95.1	60.6	58.0	66.2	30.7	66.1	68.0	69.9	36.7	38.6
Annual HIV incidence	1.65	1.86	1.68	0.21	0.56	0.64	4.43	5.95	1.75	7.81	3.72	0	4.29	15.69	1.06
HIV prevalence	25.4	22.4	21.7	11.2	31.1	11.5	44.9	21.1	10.5	13.8	18.1	5.9	8.9	30.9	8.6
Aware of HIV+ status[2]	61.8	36.0	81.6	92.8	38.8	60.1	66.8	40.8	19.6	17.8	25.8	70.3	16.6	2.4	54.6
Linked to HIV care[2]	34.0	27.1	58.2	46.0	18.8	37.8	49.2	5.4	4.4	1.7	12.1	60.3	1.7	1.3	30.0
ART use among eligible[3]	28.3	49.4	60.7	60.6	31.9	47.6	53.8	9.9	9.3	7.3	15.3	74.6	3.7	0.0	38.5
Undetectable viral load among ART eligible[3]	29.5	57.7	52.3	68.6	38.5	60.8	50.9	8.3	27.3	1.5	19.8	65.8	1.2	1.7	30.2
HIV viremia[4]	18.8	11.4	11.0	3.4	18.8	5.2	24.7	19.7	8.9	13.5	15.5	2.7	8.0	29.7	7.6
Ever tested for HCV	27.2	11.8	3.6	5.9	16.5	9.1	18.8	9.2	1.6	3.2	4.0	2.3	0.7	0.2	5.5
HCV Ab+ prevalence	64.4	50.4	9.1	4.9	64.9	15.3	41.1	48.7	51.1	42.4	25.7	7.8	22.3	63.6	34.1
Aware of HCV+ status[5]	17.4	6.2	5.5	29.7	11.7	6.1	9.2	7.3	1.4	1.5	1.8	3.1	0.1	0.6	2.9
Ever NEP use	53.0	44.5	13.5	36.2	28.0	36.1	53.0	38.9	23.8	42.1	59.2	44.3	7.7	6.8	73.8

Ever OAT	23.7	10.8	11.8	6.5	33.0	6.4	12.9	43.3	23.7	27.1	19.0	25.1	0.0	6.4	48.7
Ever shared needle/syringe	46.7	52.8	20.2	36.8	71.0	30.7	31.3	40.0	29.5	32.3	19.8	25.6	16.4	69.1	31.6
Injection drug use in prior 6 mo.	92.0	98.5	68.3	83.2	98.2	91.5	88.2	87.3	83.0	97.4	80.3	91.1	95.7	99.1	89.2

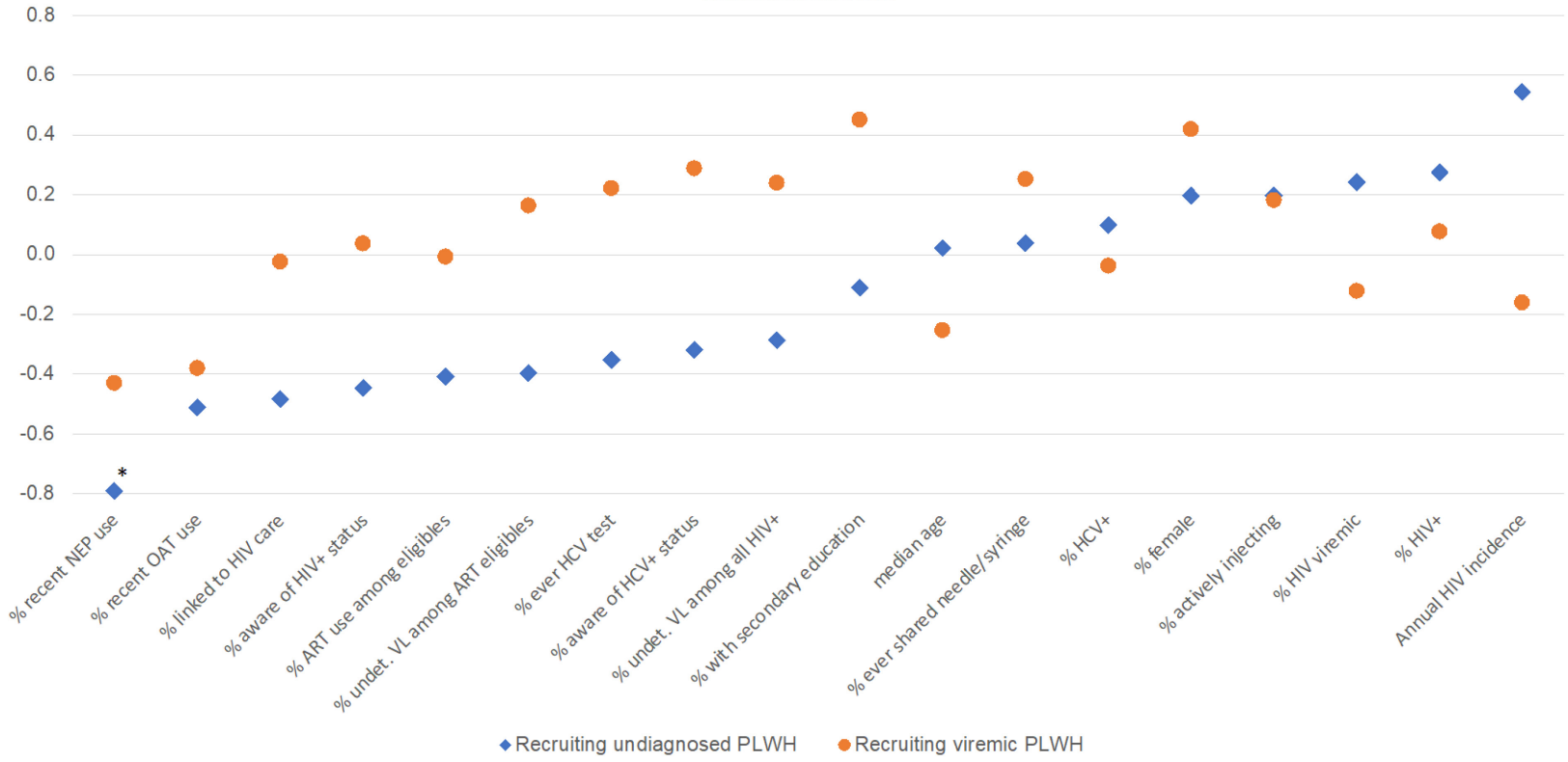
PLWH: person who inject drugs living with HIV; AZ: Aizawl; CR: Churchandpur: DM: Dimapur; GT: Gangtok; IM: Imphal; LG: Lunglei; MO: Moreh; AM: Amritsar: CD: Chandigarh: DL: New Delhi; BE: Bhubaneshwar; BI: Bilaspur: KA: Kanpur: MU: Mumbai.

*In one or more bootstrapped samples, no individuals had the outcome of interest thus the AUROC could not be calculated.

AUROC: area under the receiver operator curve from logistic regression; CI: confidence interval; ART: antiretroviral therapy; HCV: Hepatitis C virus; Ab+: antibody positive; NEP: needle/syringe exchange program; OAT: opioid agonist therapy

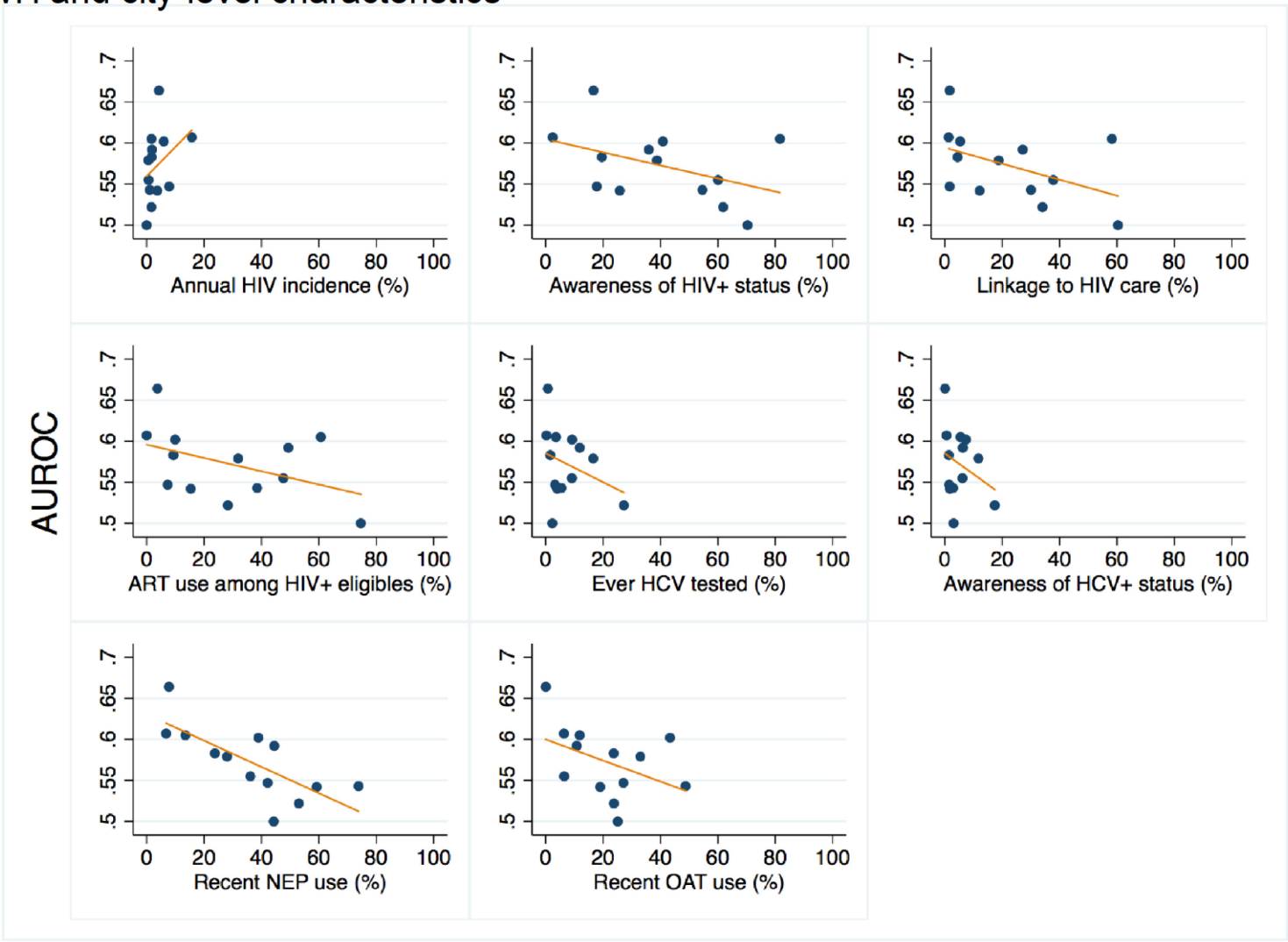
1: All city-level characteristics are RDS-II weighted with the exception of annual HIV incidence; 2: Among those HIV-infected; 3: Among those HIV-infected and CD4 count<350 or self-reported prior ART use; 4: Viral load >150 copies/mL among the whole population; 5: Among those HCV Ab positive

Figure 3.1 Correlation of multivariable model AUROC for recruiting an undiagnosed/viremic PLWH and city-level characteristics



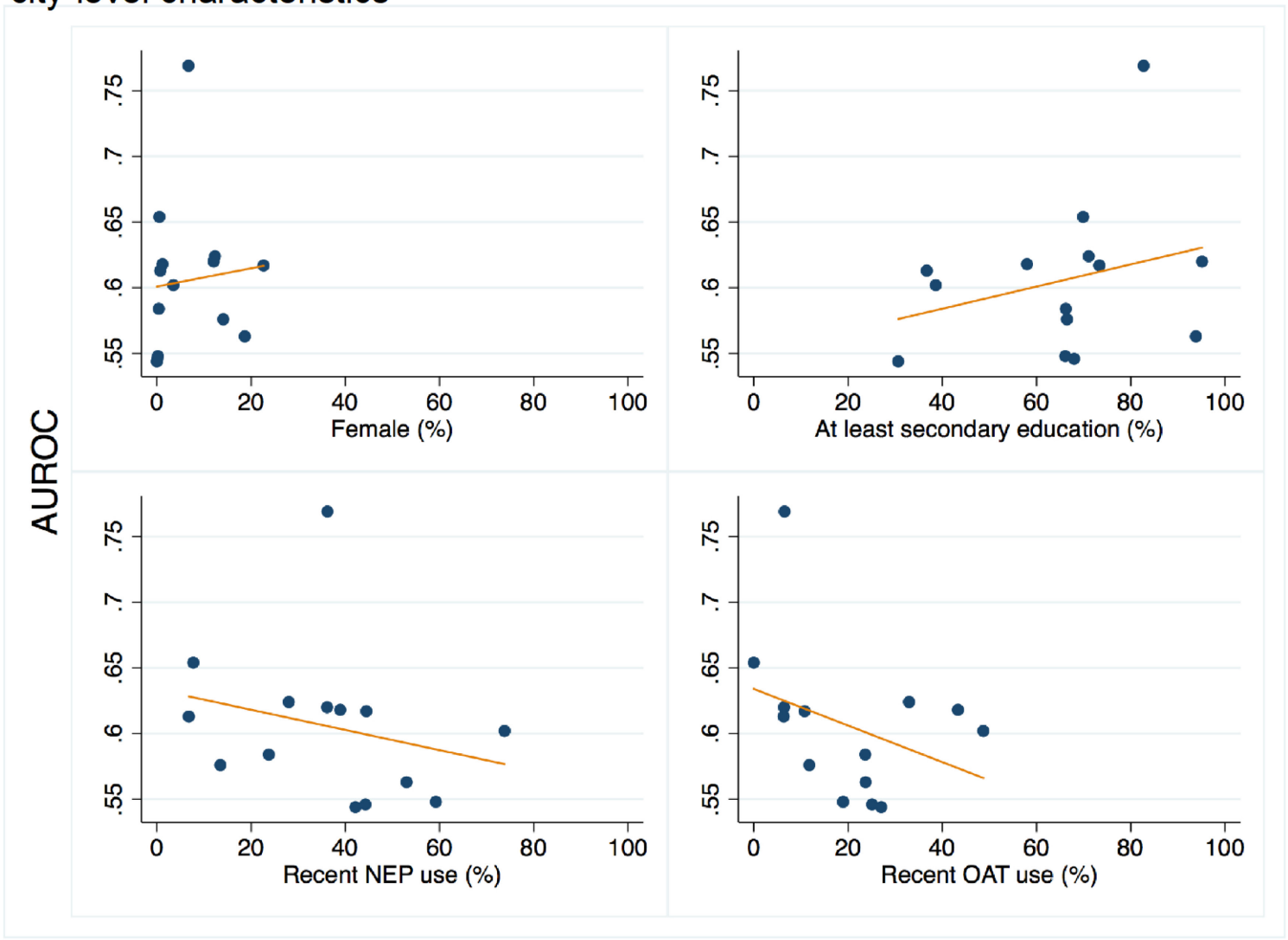
*p-value<0.05; Shaded area indicates a moderate/strong correlation
VL: HIV viral load; NEP: needle/syringe exchange program; ART: antiretroviral therapy; OAT: opioid agonist therapy

Figure 3.2a Scatterplots with linear prediction of AUROC for recruiting undiagnosed PLWH and city-level characteristics



PLWH: people who inject drugs living with HIV

Figure 3.2b Scatterplots with linear prediction of AUROC for recruiting viremic PLWH and city-level characteristics



PLWH: people who inject drugs living with HIV

Supplementary Table 3.1 Characteristics of recruiting a viremic PLWH and their predictive accuracy

Characteristic	Did not recruit viremic PLWH (N=12,659)	Recruited viremic PLWH (N=1822)						
	n (row %)/ median (IQR)	n (row %)/ median (IQR)	Odds Ratio	95% CI	AUROC	95% CI	Adjusted Odds Ratio‡	95% CI
City								
Northeast region								
Aizawl	803 (80.1)	199 (19.9)	Reference					
Churachandpur	870 (86.8)	132 (13.2)	0.61	0.48 - 0.78				
Dimapur	915 (91.3)	87 (8.7)	0.38	0.29 - 0.50				
Gangtok	979 (97.6)	24 (2.4)	0.10	0.06 - 0.15				
Imphal	833 (83.1)	169 (16.9)	0.82	0.65 - 1.03				
Lunglei	967 (96.5)	35 (4.5)	0.15	0.10 - 0.21				
Moreh	345 (75.2)	114 (24.8)	1.33	1.03 - 1.73				
North region								
Amritsar	837 (83.6)	164 (16.4)	0.79	0.63 - 0.99	0.678	0.666 - 0.690	--	
Chandigarh	900 (90.2)	98 (9.8)	0.44	0.34 - 0.57				
New Delhi	858 (85.7)	143 (14.3)	0.67	0.53 - 0.85				
Ludhiana	840 (83.8)	162 (16.2)	0.78	0.62 - 0.98				
Central region								
Bhubaneshwar	973 (97.1)	29 (2.9)	0.12	0.08 - 0.18				
Bilaspur	879 (87.7)	123 (12.3)	0.56	0.44 - 0.72				
Kanpur	735 (73.4)	267 (26.7)	1.47	1.19 - 1.81				
Mumbai	925 (92.4)	76 (7.6)	0.33	0.25 - 0.44				
Age, years (model by 10 years)	29 (24-35)	30 (25-37)	1.16	1.10 - 1.22	0.544	0.530 - 0.558	1.16	1.08 - 1.26
Gender								
Man	11,932 (87.5)	1706 (12.5)	Reference				Reference	
Woman	719 (86.1)	116 (13.9)	1.13	0.92 - 1.38	0.503	0.497 - 0.509	0.95	0.76 - 1.18
Transgender/*Hijra*	7 (100)	0 (0)	*	*			*	*
Marital status								
Never married	5305 (87.8)	740 (12.2)	Reference				Reference	
Married/long-term or living w/partner	5866 (88.0)	803 (12.0)	0.98	0.88 - 1.09	0.520	0.506 - 0.533	0.93	0.82 - 1.04
Widowed/divorced/ separated	1487 (84.2)	279 (15.8)	1.25	1.16 - 1.56			1.04	0.89 - 1.23

Characteristic	Did not recruit viremic PLWH (N=12,659)	Recruited viremic PLWH (N=1822)	Odds Ratio	95% CI	AUROC	95% CI	Adjusted Odds Ratio‡	95% CI
	n (row %)/ median (IQR)	n (row %)/ median (IQR)						
Education								
No/primary school	4303 (85.6)	723 (14.4)	Reference		0.533	0.520 - 0.546	Reference	
Secondary school	5845 (88.1)	792 (11.9)	0.81	0.72 - 0.90			0.83	0.74 - 0.93
At least high school graduate	2510 (89.1)	307 (10.9)	0.73	0.63 - 0.84			0.82	0.70 - 0.94
HIV status								
Negative	10,371 (89.8)	1182 (10.2)	Reference		0.586	0.574 - 0.597	--	
Positive	2275 (78.0)	640 (22.0)	2.47	2.22 - 2.75				
Indeterminate	12 (100)	0 (0)	*	*				
HCV status								
Negative	7956 (91.7)	725 (8.4)	Reference		0.615	0.603 - 0.627	--	
Positive	4700 (81.1)	1097 (18.9)	2.56	2.32 - 2.83				
HIV/HCV status								
HIV and HCV negative	7267 (92.5)	592 (7.5)	Reference		0.642	0.629 - 0.655	Reference	
HIV positive/HCV negative	689 (83.8)	133 (16.2)	2.37	1.93 - 2.90			2.34	1.89 - 2.90
HIV negative/HCV positive	3114 (84.1)	590 (15.9)	2.33	2.06 - 2.63			2.14	1.88 - 2.42
HIV and HCV positive	1586 (75.8)	507 (24.2)	3.92	3.44 - 4.47			3.51	3.06 - 4.04
Injection duration, years (model by 5 years)	6 (3-12)	7 (3-13)	1.07	1.03 - 1.11	0.533	0.519 - 0.547	0.93	0.89 - 0.97
Shared needle/syringe in past 6 months								
No	8437 (88.4)	1105 (11.6)	Reference		0.530	0.518 - 0.542	Reference	
Yes	4222 (85.5)	717 (14.5)	1.30	1.17 - 1.43			1.11	1.00 - 1.24
Needle/syringe exchange program use in past 6 months								
No	8287 (88.8)	1050 (11.3)	Reference		0.539	0.527 - 0.551	Reference	
Yes	4372 (85.0)	772 (15.0)	1.39	1.26 - 1.54			1.17	1.05 - 1.30
Opioid agonist therapy in past 6 months								

Characteristic	Did not recruit viremic PLWH (N=12,659)	Recruited viremic PLWH (N=1822)						
	n (row %)/ median (IQR)	n (row %)/ median (IQR)	Odds Ratio	95% CI	AUROC	95% CI	Adjusted Odds Ratio‡	95% CI
No	10,676 (87.7)	1492 (12.3)	Reference		0.512	0.503 - 0.522	Reference	
Yes	1983 (85.7)	330 (14.3)	1.19	1.05 - 1.35			1.05	0.91 - 1.20
PWID network size†								
≤8	3385 (90.8)	345 (9.3)	Reference		0.554	0.541 - 0.568	Reference	
9 to 20	362 (87.3)	529 (12.7)	1.43	1.24 - 1.65			1.25	1.08 - 1.45
21 to 50	3054 (86.7)	467 (13.3)	1.50	1.29 - 1.74			1.23	1.06 - 1.43
≥51	2596 (84.4)	481 (15.6)	1.82	1.57 - 2.11			1.37	1.17 - 1.60

PLWH: person who injects drugs living with HIV; IQR: interquartile range; CI: confidence interval; AUROC: area under the receiver operator curve; HCV: Hepatitis C virus; PWID: person who injects drugs

‡Adjusted for all other covariates listed below; *Predicted the outcome perfectly and was thus dropped from the regression model; †Number of PWID they personally know in their city, categorized by quartile

Chapter 4: Identifying undiagnosed HIV-infected people who inject drugs using respondent-driven sampling

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ABSTRACT

Background People who inject drugs (PWID) experience a high HIV burden and lag behind in meeting the UNAIDS 90-90-90 continuum target, particularly at diagnosis. In prior work, respondent-driven sampling (RDS), a type of chain referral sampling, rapidly identified undiagnosed HIV-infected PWID in India. The objective of this paper is to evaluate whether the efficiency of identification of undiagnosed HIV-infected PWID in India can be further enhanced through alterations to the RDS coupon system.

Methods First, we identified characteristics that predict recruitment of an undiagnosed HIV-infected PWID into an RDS, using RDS data from 4,002 PWID in four north Indian cities in 2013. The area under the receiver operator curve (AUROC) from logistic regression models and a random forest were used to identify predictors and a multivariable prediction model was built. An altered coupon system was tested using RDS data from 1289 PWID in Morinda, Punjab. RDS participants were randomly assigned (1:1) to a normal or altered coupon system. In the normal system, PWID received 2 recruitment coupons. In the altered system, the prediction model determined their likelihood of recruiting an undiagnosed HIV-infected PWID; those likely received 5 coupons, those unlikely received 2 coupons. The number needed to recruit (NNR) - average number of individuals recruited in order to find one undiagnosed individual - for recruits of each coupon system was used to compare the efficiency of the two systems.

Results Predictors of recruiting an undiagnosed HIV-infected PWID identified by the AUROCs and random forest included HIV/HCV infection, PWID network size, utilization of needle/syringe exchange programs, and the injection environment - where PWID and with whom

they inject. In Morinda, median age of the sample was 27, all were men, and 22% injected daily. HIV prevalence was 11%, of whom 66% were previously undiagnosed. Among recruits, 643 were randomized to the normal system, from which 475 PWID were recruited, including 29 undiagnosed; 646 were randomized to the altered coupon system, from which 810 were recruited, including 65 undiagnosed. The NNR for the normal coupon system was 16.4 compared to an NNR of 12.5 for the altered system (difference=3.9, 95% CI: -1.6 to 13.1).

Conclusions An altered RDS coupon system in which individuals more likely to recruit undiagnosed HIV-infected PWID were provided more recruitment coupons did not significantly improve the efficiency of identification of undiagnosed PWID over the normal/traditional coupon system in which all participants receive the same number of coupons.

INTRODUCTION

Diagnosis is the first step in the HIV care continuum and is required in order to link people living with HIV (PLWH) to the care and treatment they need[1]. The importance of this step to individual and community benefit is highlighted in the UNAIDS 90-90-90 target to help end the global AIDS epidemic by 2020 - 90% of PLWH diagnosed, 90% of those diagnosed receiving sustained antiretroviral therapy (ART), and 90% of those on ART virally suppressed [2]. Along with maximizing evidence-based prevention efforts, treating a large majority of PLWH will avert new infections. All of this must occur in a human rights framework, including respecting the unique needs of key populations such as men who have sex with men (MSM), people who inject drugs (PWID), and sex workers. For these populations, structural factors such as stigma, discrimination, and criminalization often make accessing HIV prevention and care services difficult thus leading to large gaps in the continuum - particularly at diagnosis[3]. Among PWID in India, we previously found only 40% of those HIV-infected were aware of their infection, well behind the 90% target[4].

Narrowing these gaps and meeting the UNAIDS first 90 target (HIV diagnosis) will require new approaches to reach those not currently engaged in HIV testing services. Looking to existing tools and investigating how to leverage or alter them to identify more undiagnosed PLWH is a good first step, especially given our current landscape of limited or declining investment and resources. Respondent-driven sampling (RDS), a type of chain-referral sampling, is commonly used in public health for HIV surveillance and research among key populations for which a sampling frame does not exist[5]. Using recruitment coupons distributed to peers, RDS leverages social network connections to recruit study participants, rather than utilizing study staff to

identify and recruit potential participants. While the resulting sample is most likely biased, specifically designed estimators can weight estimates to provide unbiased population estimates such as HIV prevalence. Recently, several have noted the potential of RDS to be used beyond surveillance or measuring population characteristics to an implementation tool or intervention to quickly reach and engage individuals at high-risk for HIV[6-9]. In prior work, we found RDS rapidly identified PWID in India, including many that were HIV-infected but previously undiagnosed or viremic - individuals not engaged in traditional HIV services such as clinic-based HIV testing and care or outreach services[10]. Given the potential of RDS to be used as a strategy to improve levels of diagnosis among PLWH, the overall objective of this paper is to evaluate whether the efficiency of identification of undiagnosed HIV-infected PWID in India can be further enhanced through alterations to the RDS coupon system.

METHODS

Overview

The evaluation of an altered RDS coupon system was conducted in Morinda, Punjab, located in the northern region of India. To design the altered system, we first identified characteristics that predict recruitment of an undiagnosed HIV-infected PWID into an RDS. Since there is significant regional variation in HIV prevalence and incidence, care continuum outcomes, and injection drug use characteristics across India, RDS data from sites in northern India included in a prior study were used to build a prediction model. This model was then used to determine differential coupon distribution in the evaluation of the altered RDS coupon system in Morinda. Detailed methods are described below.

Predicting recruitment of an undiagnosed HIV-infected PWID

Study design and procedures

To identify characteristics that predict recruitment of an undiagnosed HIV-infected PWID, data from the National Collaboration on AIDS (NCA) trial (ClinicalTrials.gov identifier: NCT01686750) were used. The NCA trial is a cluster-randomized trial among MSM and PWID in India investigating the community effectiveness of integrated care centers (ICCs) on the uptake of HIV testing as previously described[11]. Population-level effectiveness was assessed using two community cross-sectional samples collected via RDS before and after implementation of ICCs. Data for this analysis were restricted to the pre-intervention (or baseline) data collected from four cities located in northern India in the PWID stratum of the trial (Amritsar, Ludhiana, Chandigarh, and New Delhi) (**Figure 1**).

Participants were recruited using RDS between January and July 2013. Two seeds, individuals considered to be well-connected and influential in the local PWID community, initiated recruitment in each city. Each seed received two recruitment coupons to distribute randomly to others they know inject drugs in the community. Individuals that received a coupon, voluntarily visited the study center, and if eligible, were enrolled, completed study procedures, and received two recruitment coupons to distribute to their network at random. Recruitment continued until the desired sample size in each city was met (~1000 recruits). Coupons were bar-coded with identification numbers to link recruiters and their recruits and included a hologram to prevent duplication of coupons. Eligibility criteria to enroll in the study included (1) being at least 18 years old, (2) provision of informed consent, (3) possession of a valid coupon unless a seed, and (4) self-reported injection drug use in the prior 24 months. Dual compensation was provided for

study participation and recruitment. Study participants received INR 250 (US $3.8) for completing study procedures and INR 50 (US $0.80) for each eligible study participant they recruited into the study.

After informed consent was obtained, study participants provided a blood sample and completed an interviewer-administered questionnaire that collected socio-demographics, HIV and HCV testing and care history, injection and sexual HIV risk behaviors, harm reduction services utilization, and network characteristics. HIV pre- and post-test counseling in addition to appropriate referrals to care for HIV-infected participants were provided with rapid onsite HIV testing. HIV testing was conducted in accordance with Indian guidelines using 3 rapid tests: Alere Determine 1/2 (Alere Medical, Chiba, Japan), First Response HIV Card Test 1-2.0 (Premier Medical Corporation, Daman, India), and Signal Flow Through HIV 1+2 Spot/Immunodot Test Kit (Span Diagnostics, Surat, India). HIV-1 RNA (viral load) quantification was conducted for all HIV-infected participants using Abbott RealTime HCV assay (Abbott Laboratories, Abbott Park, Illinois, US). Hepatitis C (HCV) antibody testing was conducted on stored blood samples using Genedia HCV ELISA 3.0 (Green Cross Medical Science, Chungbuk, Korea).

Statistical methods

NCA study participants were categorized as undiagnosed if positive by the rapid HIV tests and self-reported no prior diagnosis. For each participant, we determined whether they recruited an undiagnosed PWID into the RDS - the main outcome of interest - using the linkage between recruiters and their recruits in the data. If a participant recruited at least one undiagnosed PWID

out of their enrolled recruits, they were considered to have the outcome of interest (Y=1) and participants that recruited no undiagnosed PWID or had no recruits at all did not have the outcome (Y=0). Characteristics that predict recruitment were identified using two methods: logistic regression models and a random forest. Characteristics investigated included HIV infection status as well as those shown to be associated with HIV risk among PWID in the literature including socio-demographics, HCV infection status, sexual and injection drug use risk behaviors, and network size. In total, the predictive ability of more than 50 characteristics were explored.

Univariable logistic regression models were conducted for each characteristic of interest and the area under the receiver operator curve (AUROC) was calculated to discriminate between those that do and do not recruit undiagnosed HIV-infected PWID. AUROCs were calculated using a 10-fold cross-validation technique to address over fitting of the model[12]. To briefly describe this technique, the full data were randomly divided into ten evenly sized groups; one group was left out as the validation set and the logistic model was run on the remaining nine groups (i.e., the training group). Model coefficients were then applied to the validation set data. This is repeated so that each group was in the training group nine times and the validation data once. Predicted probabilities from the validation model were used to calculate the overall AUROC.

In addition to the regression models, a random forest was built to assess characteristics' predictive ability. Briefly, a random forest is a machine learning algorithm that can be used for regression (i.e., continuous outcome) or classification (i.e., categorical outcome) purposes[13]. For this analysis, we used classification since the outcome is dichotomous. First, a bootstrapped

sample with replacement of the full data set was conducted; this new data set is known as the in-bag data. With the in-bag data, a decision tree was constructed using a random selection of variables at each node of the tree starting at the root node (number of candidate variables assessed at each node=$\sqrt{m}$, where m=number of total predictor variables); the variable with the best split was chosen and splits continued to occur until a decision node resulted in a completely homogenous sample (i.e., all observations have the same classification). A large number of decision trees are often made with the in-bag data, generally hundreds, hence the term *forest*. Then, each observation in the out-of-bag data (i.e., those not in the in-bag data) was run down each tree which gave a predicted classification (i.e., vote). The classification with the most votes across the trees was the classification for that observation and with this information, an error rate for the out-of-bag classification can be calculated. Variable importance (VIMP) can be calculated for each characteristic, which represents how much removing the characteristic reduces the accuracy of the model - or increases the error rate. The random forest constructed for predicting recruitment of an undiagnosed HIV-infected PWID included 56 different characteristics and 500 trees. The best split at each node in the tree was determined by the Gini index. Variable importance was calculated for each characteristic using the permutation method[13].

A multivariable prediction model was built that included characteristics with an AUROC>0.5 from the univariable logistic regression *or* a VIMP>0 from the random forest. An overall AUROC was calculated for the prediction model to determine its ability to discriminate between those that do and do not recruit an undiagnosed HIV-infected PWID. For the altered RDS coupon system in Morinda, a cut-point in predicted probability calculated from the prediction

model was required to divide the sample into two groups: 1) likely to recruit an undiagnosed HIV-infected PWID and 2) unlikely to recruit an undiagnosed HIV-infected PWID. Sensitivity and specificity of the probabilities were calculated to assess the ideal cut-point which was chosen so that sensitivity was optimized while ensuring specificity was at least 0.5.

Evaluating alterations to the RDS recruitment coupon system

Study design and procedures

To evaluate whether the efficiency of identification of undiagnosed HIV-infected PWID can be enhanced through alterations to the RDS coupon system, data were collected as a part of a study designed to identify cost-effective network and geospatial strategies to identify PWID across several different Indian cities. For this analysis, we used data from Morinda, Punjab, a small city located in northern India and situated on the main road connecting Chandigarh and Ludhiana (**Figure 1**). In Morinda, we evaluated a targeted time-based RDS (ttRDS) strategy, a variation of RDS in which RDS was allowed to run for a year, regardless of sample size accrued, and a targeted or altered RDS recruitment coupon system was implemented and compared to a normal coupon system in terms of the systems' efficiency of identification of undiagnosed HIV-infected PWID.

In December 2017, two seeds initiated recruitment in Morinda and each received two recruitment coupons to distribute randomly to others they know inject drugs in the community. Then beginning at the first wave of recruitment and beyond (i.e., recruits of the seeds, recruits of wave 1, etc.), individuals were randomized to one of two arms, the normal coupon system or the altered coupon system, in a 1:1 allocation (**Figure 2**). Prior to implementation, a randomization

list was made with blocks of varying sizes (8 to 16). If randomized to the normal coupon system, they received two recruitment coupons to distribute to their network. If randomized to the altered coupon system, a software program extracted the individual's specific questionnaire responses from the interview as well as the rapid HIV and HCV test results into the prediction model (multivariable logistic regression model including all characteristics with AUROC>0.5 *or* VIMP>0 as described above) and calculated the predicted probability of recruiting an undiagnosed HIV-infected PWID. If the predicted probability was below the cut-point (cut-point determined as previously described above) the person received two recruitment coupons to distribute to their network, and if greater than or equal to the cut-point, they received five recruitment coupons.

As in the NCA trial, coupons were bar-coded with identification numbers to link recruiters and their recruits and included a hologram to prevent duplication of coupons. Eligibility criteria to enroll in the study was the same as the NCA trial with the exception of the last criterion: self-reported injection drug use in the prior *12* months (as opposed to 24 months for the NCA trial). The same dual compensation was provided for study participation and recruitment as in the NCA trial. A biometric system was used to track duplicate enrollments into the RDS as well as identify individuals that were clients of nearby ICCs and/or participated in our prior RDS samples in the region in 2016-2017. Clients' fingerprints were scanned then converted into unique alphanumeric codes using proprietary software; codes could not be converted back to fingerprint images.

Following consent, study participants provided a blood sample and completed an interviewer-administered questionnaire that collected socio-demographics, HIV and HCV testing and care history, injection and sexual HIV risk behaviors, harm reduction service utilization, and network characteristics. HIV/HCV pre- and post-test counseling with appropriate referrals to care for infected participants were provided with rapid onsite HIV and HCV testing. HIV testing was conducted in accordance with Indian guidelines using 3 rapid tests as in the NCA trial. Onsite HCV antibody testing was conducted using SD BIOLINE HCV (Standard Diagnostics, Inc, Korea).

Statistical methods

Preliminary data available through September 11, 2018 were analyzed. For exploratory data analyses, overall sample characteristics, recruit characteristics by coupon system and number of recruitment coupons received, and RDS process measures are described including total number of recruitment waves and coupon return rate. Statistical comparisons of characteristics between groups used chi-squared tests for categorical variables and the Wilcoxon rank-sum test for continuous variables.

The number needed to recruit (NNR) in order to find one undiagnosed individual (total number recruited / number of undiagnosed PWID identified) was used to compare the efficiency of the two coupon systems - normal vs. altered - in identifying undiagnosed HIV-infected PWID. The lower the NNR, the more efficient a system. The NNR was calculated for the recruits of each coupon system. Using the link between recruiter and recruit in the data, we identified each study participant's recruiter and which arm they were in. Then, the NNR was calculated for the recruits

of each coupon system (excluding wave 1 participants since their recruiters were seeds). The difference in the NNR between the two systems was calculated and a confidence interval around the difference was estimated using a bootstrap method. For the recruits of each coupon system separately, 1000 samples with replacement of the data were taken. For each sample, the NNR for each arm was calculated and the resulting NNR difference. The 2.5th and 97.5% percentile of the 1000 NNR differences represent the 95% confidence interval. As a secondary analysis, we explored the NNR over time, by month of active cumulative recruitment, for the two coupon systems. As an additional efficiency measure, we calculated the identification rate, which is the average number of undiagnosed individuals identified per week (total number of undiagnosed HIV-infected PWID identified / total number of weeks RDS recruitment was active), by recruiter's coupon system. The confidence interval for the difference in identification rate between the two systems was calculated using a bootstrap method similar to the one used for the NNR difference as described above.

Analyses were conducted using Stata (StataCorp. 2017. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC) with the exception of the random forest and VIMP calculation in which the package randomForestSRC in R was used (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). P-values were considered statistically significant at <0.05.

Ethical clearances

This study was approved by the institutional review boards of Johns Hopkins University School of Medicine and the Y.R. Gaitonde Centre for AIDS Research and Education.

RESULTS

Predicting recruitment of an undiagnosed HIV-infected PWID

A total of 4,002 study participants were recruited across the four north NCA trial sites. Median age was 28 (interquartile range [IQR]: 23 - 35), nearly all were male (99.7%), 52.6% were never married, 7.6% were widowed/divorced/separated, and 45.4% had a primary education or less. More than half were injecting daily (52.3%) and of those actively injecting in the prior months, 79.7% reported injecting buprenorphine, the most commonly used drug. HIV prevalence among the sample was 18.5%; 72.8% of those infected were previously unaware of their status. HCV prevalence was 46.8%. The overall coupon return rate was 50.1%; 42.2% recruited no participants into the RDS, 15.9% recruited one PWID, and 42.0% recruited two PWID into the RDS. Among all study participants, 12.1% recruited at least one undiagnosed HIV-infected PWID.

Characteristics of recruiting an undiagnosed HIV-infected PWID are presented in **Table 4.1** along with their predictive accuracy calculated from univariable logistic regressions (i.e., AUROC) and the random forest (i.e., VIMP). The larger an individual's PWID network size, the more likely they were to recruit an undiagnosed PWID (by an increase of one ln OR: 1.10, 95% CI; 1.03 - 1.18); network size had the highest AUROC (0.534). Compared to those HIV and HCV negative, PWID with mono-HCV infection (OR: 1.38, 95% confidence interval [CI]: 1.11 - 1.71) and co-infection (OR: 1.78, 95% CI: 1.37 - 2.31) were significantly more likely to recruit

an undiagnosed PWID; HIV/HCV status had the second highest AUROC (0.531). Other characteristics with an AUROC>0.5 included the number of sexual partners in the prior six months (AUROC=0.509), injecting buprenorphine in the prior six months (AUROC=0.510), injecting in a shooting gallery in the prior six months (AUROC=0.504) and using a needle/syringe exchange program (NEP) in the prior six months (AUROC=0.522). Demographics - age, sex, marital status, and education - were not significantly associated with recruiting an undiagnosed PWID. HIV/HCV status, NEP use, and injecting in a shooting gallery also had VIMP scores above one. Characteristics with VIMP scores above one but that did not have an AUROC>0.5 include injecting sedatives (VIMP=0.000638) and stimulants (VIMP=0.000134) in the prior six months, injecting with multiple people (VIMP=0.000447) and sexual partners (VIMP=0.000179) in the prior six months, being incarcerated in the prior six months (VIMP=0.000134), injecting at a friend's house (VIMP=0.000134), public toilet (VIMP=0.000045) or other place (VIMP=0.000078) in the prior six months, and being female (VIMP=0.000022).

The multivariable model including only characteristics with an AUROC>0.5 resulted in an AUROC of 0.573 (**Table 4.2**); adding the characteristics identified by the random forest with a VIMP>0 increased the AUROC to 0.575. **Figure 3** plots the sensitivity and specificity of probability cut-offs from the multivariable model including all characteristics with an AUROC>0.5 or VIMP>0 (i.e., the final prediction model used for evaluating the altered RDS coupon system in Morinda). A probability cut-off of approximately 0.11 results in a sensitivity of 0.65 and specificity of 0.50 and therefore was chosen as the cut-off to be used in Morinda. This cut-off results in a positive predictive value of 0.16 and negative predictive value of 0.92.

Evaluating alterations to the RDS recruitment coupon system

As of September 11, 2018, 1289 PWID recruits were enrolled and completed study procedures in Morinda. Median age was 27 (IQR: 22 - 33), all were men, 21.5% were injecting daily and among those injecting in the prior six months, the most commonly used drug was buprenorphine (77.5%). HIV prevalence was 11.0% and 66.2% of those HIV-infected were previously unaware of their infection. HCV prevalence was 44.8% and HIV/HCV co-infection was 9.8%. Forty (3.1%) had a biometric match to an ICC client, nearly all in Chandigarh (n=38) and 31 (2.4%) matched to a recent RDS participant, nearly all in Chandigarh (n=29).

Among recruits, 643 were randomized to the normal coupon system and 646 were randomized to the altered coupon system. Characteristics were similar across the two arms/coupon systems (**Table 4.3**). Of those in the altered system, 307 (47.5%) had a predicted probability less than 0.11 and received two recruitment coupons; 339 (52.5%) had a predicted probability of at least 0.11 and received 5 coupons. Applying the prediction model built using the NCA trial data to the RDS data in Morinda, the AUROC was 0.621 (95% CI: 0.570 - 0.672), suggesting good predictive ability.

Recruitment progressed to 17 waves. Most participants were generated from one of the seeds (97.6%) (**Figure 4**). The overall coupon return rate was 35.7% and did not differ across study arms/coupon systems (normal coupon system arm=36.9%, altered coupon system arm=35.1%, altered-two coupon=36.0%, altered-five coupon=34.7%). On average, those that received two

coupons (in either arm), recruited 0.7 participants. For those in the altered arm that received 5 coupons, they recruited 1.8 participants on average.

From the normal coupon system, a total of 475 PWID were recruited and from the altered system, a total of 810 were recruited. There were no significantly different characteristics across the recruits of the two coupon systems (**Table 4.3**). Within recruits of the altered system, there were some significant differences between participants that were recruited by those determined to be less likely to recruit an undiagnosed PWID (i.e., predicted probability<0.11 and received 2 coupons) and those determined to be more likely to recruit an undiagnosed PWID (i.e., predicted probability≥0.11 and received 5 coupons). Recruits of those that received 5 coupons were more likely to have been tested for HIV in the prior year (39.7% vs. 22.6%, p<0.001) and use a needle/syringe exchange program (36.7% vs. 28.1%, p=0.021) or opioid agonist therapy (31.2% vs. 20.4%, p=0.002) in the prior six months. When compared to recruits of those randomized to normal coupon system that had a predicted probability≥0.11 (i.e., would have received more recruitment coupons had they been randomized to the altered system), recruits of those that received 5 coupons were similar across all characteristics explored with the exception of number of sexual partners in the prior six months. Recruits of those that received 5 coupons were more likely to have 1 sexual partner (52.1% vs. 42.9%, p=0.022) (**Supplementary Table 4.1**).

A total of 29 undiagnosed HIV-infected PWID were recruited from the normal system, resulting in an NNR of 16.4. A total of 65 undiagnosed PWID were recruited from the altered system, resulting in an NNR of 12.5. The difference in NNR was 3.9 but the confidence interval overlaps zero (95% CI: -1.6 to 13.1), therefore the difference is not statistically significant. Plotting the

NNR over recruitment months suggests that the normal coupon system NNR generally decreased over time while the altered coupon system NNR seemed to be more stable (**Supplementary Figure 4**). At each time point the difference in NNR between the two systems was not statistically significant (i.e., confidence interval of difference overlapped zero). The identification rate of undiagnosed HIV-infected PWID for the altered system was higher (1.7/week) than the normal system (0.8/week) (difference: 0.9, 95% CI: 0.4 - 1.4).

DISCUSSION

An altered RDS coupon system in which individuals more likely to recruit undiagnosed HIV-infected PWID were provided more recruitment coupons did not significantly improve the efficiency of identification of undiagnosed PWID over the traditional coupon system. Characteristics such as HIV and HCV infection, PWID network size, utilization of needle/syringe exchange programs, and the injection environment - where PWID and with whom they inject - predicted who was more likely to recruit undiagnosed PWID. However, characteristics' predictive ability was generally quite low, suggesting recruitment and/or the network composition among our target population did not have strong enough patterns to steer an RDS to more efficiently identify undiagnosed PWID.

On the other hand, the number of undiagnosed PWID identified each week was significantly higher for the altered coupon system, finding almost one additional undiagnosed person each week over the normal system and more than twice as many in total over the full recruitment period of 10 months. This was a consequence of more coupons given and recruits enrolled from the altered system. Increasing the number of recruitment coupons more rapidly identified PWID

overall, which often results in RDS recruitment trees that grow out (or wide), rather than down. This may result in samples that do not reach deeper into the network, not reaching those more peripheral that have different risk profiles from the seeds or earlier waves, which would have consequences for the ability of the sample to provide unbiased population estimates[14]. However, recruits of the two systems did not differ on key risk behaviors or other characteristics and, importantly, the goal of the altered system was to increase the efficiency of identifying undiagnosed HIV-infected PWID, not estimate population characteristics. Statistical methods that take data from an RDS sample that has been deliberately steered to a particular sub-group and estimate population characteristics such as HIV prevalence should be an area of future research.

There is little prior research on differential coupon distribution in order to steer an RDS sample to preferentially recruit specific sub-groups. Among PWID in Tijuana, Mexico, researchers provided more coupons to women in order to recruit more women but were not successful[15]; notably, this strategy assumes women who inject drugs are connected to other women, which may not be the case. Similar to differential coupons, researchers have increased participant compensation for recruiting more of a particular sub-group such as younger PWID[14] or individuals at high risk for HIV[16] in the United States, with the former but not the latter being successful. In Tajikistan, Kan and colleagues compared a traditional RDS design in which recruitment of PWID continued indefinitely to a system in which recruitment ceased after two waves with no HIV-infected PWID in terms of the approaches' ability to identify new HIV diagnoses; the restricted RDS approach yielded more new diagnoses[17]

It is important to note that Morinda is a smaller community compared to the others that we have previously conducted RDS samples in for the NCA trial, likely with a smaller total population size of PWID. There are currently approximately 400 PWID registered at the local OAT center (per personal communication), so with over 1200 total PWID recruited, we may have sampled a large fraction of PWID in Morinda and its surrounding communities. This may have impacted our ability to see a meaningful and/or statistically significant difference between the two coupon systems. To investigate possible implications, future work will explore the geographical reach of the RDS using pin code as well as calculate PWID population size estimates.

There are limitations to this work that should be noted. First, the evaluation was conducted in one city in India. Replicating this or a similar approach in additional communities with different HIV and injection drug use epidemics would provide more robust evidence on the efficiency of an altered RDS coupon system among PWID. Awareness of HIV infection was self-reported using an interviewer-administered questionnaire, which is subject to recall or reporting bias, though well-trained interviewers are used to mitigate bias. Validating self-reported diagnosis status with local testing centers in Morinda was not be feasible. However, incorporating HIV plasma viral load data, when available, can assess the number of individuals that are likely already diagnosed and on ART (i.e., have an undetectable viral load) but do not self-report being aware of their infection.

In summary, getting to the UNAIDS 90-90-90 target will require novel strategies to reach the more hidden or difficult-to-reach people living with HIV (PLWH) that are not currently engaged in HIV testing and care services. RDS, already employed in HIV research and surveillance,

could be leveraged to reach undiagnosed PLWH, especially in key populations such as PWID and MSM who are stigmatized and often more difficult-to-reach populations that lag behind in the reaching the UNDAIDS target. While differential coupon distribution did not significantly increase the efficiency of identifying undiagnosed HIV-infected PWID, RDS or similar network-driven strategies should still be considered alongside other strategies to ensure the UNAIDS first 90 target is reached for all populations living with HIV.

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Table 4.1 Characteristics of recruiting an undiagnosed HIV-infected PWID and their predictive accuracy

Characteristic	Did not recruit undiagnosed PWID (N=3516) n (col %)/ median (IQR)	Recruited undiagnosed PWID (N=486) n (col %)/ median (IQR)	Odds Ratio	95% CI	AUROC	95% CI	VIMP
Socio-demographics							
City							
Amritsar	880 (25.0)	121 (24.9)	Reference				
Chandigarh	905 (25.7)	93 (19.1)	0.75	0.56 - 0.99	--	--	--
New Delhi	874 (24.9)	127 (26.1)	1.06	0.81 - 1.38			
Ludhiana	857 (24.4)	145 (29.8)	1.23	0.95 - 1.59			
Age, years (model by 10 years)	28 (23 - 35)	29 (23 - 36)	1.06	0.96 - 1.17	0.499	0.471 - 0.527	-0.00499
Female (model vs. male/*hijra*)	12 (0.3)	2 (0.4)	1.21	0.27 - 5.41	0.457	0.430 - 0.484	0.00002
Marital status							
Never married	1828 (52.0)	275 (56.6)	Reference				
Married/long-term or living w/partner	1418 (40.3)	179 (36.8)	0.84	0.69 - 1.03	0.495	0.468 - 0.523	-0.00189
Widowed/divorced/separated	270 (7.7)	32 (6.6)	0.79	0.53 - 1.16			
Education							
No/primary school	1594 (45.3)	221 (45.5)	Reference				
Secondary school	1413 (40.2)	206 (42.4)	1.05	0.86 - 1.29	0.490	0.464 - 0.517	-0.00308
At least high school graduate	509 (14.5)	59 (12.1)	0.84	0.62 - 1.13			
HIV/HCV characteristics							
Tested for HIV in prior year	1180 (33.6)	166 (34.2)	1.07	0.88 - 1.31	0.495	0.467 - 0.523	-0.00133
HIV positive	623 (17.7)	119 (24.5)	1.50	1.20 - 1.88	0.502	0.473 - 0.531	--
HIV status and diagnosis							
HIV negative	2893 (82.3)	367 (75.5)	Reference				
HIV positive, undiagnosed	456 (13.0)	84 (17.3)	1.45	1.12 - 1.88	0.502	0.474 - 0.531	-0.00125
HIV positive, diagnosed	167 (4.8)	35 (7.2)	1.65	1.13 - 2.42			
HIV status and viral load							
HIV negative	2896 (82.4)	367 (75.5)	Reference				
HIV positive, undetectable	70 (2.0)	10 (2.1)	1.13	0.58 - 2.21	0.497	0.468 - 0.526	--
HIV positive, detectable	550 (15.6)	109 (22.4)	1.56	1.24 - 1.97			
HCV positive	1606 (45.7)	268 (55.1)	1.46	1.21 - 1.77	0.520	0.492 - 0.547	--
HIV/HCV status							

Characteristic	Did not recruit undiagnosed PWID (N=3516) n (col %)/ median (IQR)	Recruited undiagnosed PWID (N=486) n (col %)/ median (IQR)	Odds Ratio	95% CI	AUROC	95% CI	VIMP
HIV and HCV negative	1794 (51.0)	199 (41.0)	Reference				
HIV positive/HCV negative	116 (3.3)	19 (3.9)	1.48	0.89 - 2.45	0.531	0.503 - 0.559	0.00049
HIV negative/HCV positive	1099 (31.3)	168 (34.6)	1.38	1.11 - 1.71			
HIV and HCV positive	507 (14.4)	100 (20.6)	1.78	1.37 - 2.31			
Sexual risk behaviors							
Lifetime sexual partners							
None	455 (12.9)	81 (16.7)	Reference				
1 or 2	1095 (31.1)	148 (30.5)	0.76	0.57 - 1.02			
3 to 7	1155 (32.9)	162 (33.3)	0.79	0.59 - 1.05	0.500	0.472 - 0.527	-0.00012
8 to 17	459 (13.1)	53 (10.9)	0.65	0.45 - 0.94			
18 or more	352 (10.0)	42 (8.6)	0.67	0.45 - 1.00			
Sexual partners in prior 6 mo.							
None	1698 (48.3)	261 (53.7)	Reference				
1	1282 (36.5)	164 (33.7)	0.83	0.68 - 1.03	0.509	0.482 - 0.536	-0.00175
2 or more	536 (15.2)	61 (12.6)	0.74	0.55 - 0.99			
No sexual partners in prior 6 mo.	1698 (48.3)	261 (53.7)	1.24	1.03 - 1.50	0.506	0.479 - 0.534	--
Unprotected sex in prior 6 mo.							
No	439 (12.5)	56 (11.5)	Reference				
Yes	1379 (39.2)	169 (34.8)	0.96	0.70 - 1.32	0.500	0.472 - 0.527	-0.00019
No sexual partners	1698 (48.3)	261 (53.7)	1.21	0.89 - 1.64			
Substance use risk behaviors							
Alcohol use (AUDIT)							
Low/moderate use	1990 (56.6)	288 (59.3)	Reference				
Harmful/hazardous use	612 (17.4)	94 (19.3)	1.06	0.83 - 1.36	0.493	0.467 - 0.520	-0.00148
Alcohol dependence	914 (26.0)	104 (21.4)	0.79	0.62 - 1.00			
Drugs ever injected							
Heroin only	253 (7.2)	17 (3.5)	Reference				
Buprenorphine/other pharmaceuticals only	2049 (58.3)	322 (66.3)	2.34	1.41 - 3.88	0.513	0.487 - 0.538	-0.00149
Combination	1208 (34.4)	147 (30.3)	1.81	1.08 - 3.05			
Injection drug use frequency in prior 6 mo.							

Characteristic	Did not recruit undiagnosed PWID (N=3516) n (col %)/ median (IQR)	Recruited undiagnosed PWID (N=486) n (col %)/ median (IQR)	Odds Ratio	95% CI	AUROC	95% CI	VIMP
None	443 (12.6)	55 (11.3)	Reference				
Less than daily	1243 (35.4)	167 (34.4)	1.08	0.78 - 1.50	0.485	0.457 - 0.513	-0.00031
Daily	1830 (52.1)	264 (54.3)	1.16	0.85 - 1.58			
Shared needle/syringe in prior 6 mo.	992 (28.2)	137 (28.2)	1.00	0.81 - 1.23	0.449	0.422 - 0.476	-0.00067
Drugs injected in prior 6 mo.:							
Heroin	835 (23.8)	91 (18.7)	0.74	0.58 - 0.94	0.489	0.463 - 0.514	-0.00054
Buprenorphine	2420 (68.8)	371 (76.3)	1.46	1.17 - 1.82	0.510	0.483 - 0.536	-0.00120
Stimulants	15 (0.4)	3 (0.6)	1.45	0.42 - 5.03	*	*	0.00013
Sedatives	431 (12.3)	68 (14.0)	1.16	0.88 - 1.53	0.473	0.445 - 0.501	0.00064
Place injected in prior 6 mo.:							
Home	752 (21.4)	95 (19.6)	0.89	0.70 - 1.13	0.478	0.451 - 0.505	-0.00031
Friend's house	752 (21.4)	94 (19.3)	0.88	0.69 - 1.12	0.482	0.455 - 0.508	0.00013
Public park/playground	1809 (51.5)	238 (49.0)	0.91	0.75 - 1.09	0.486	0.459 - 0.513	-0.00041
Public toilet	822 (23.4)	107 (22.0)	0.93	0.74 - 1.16	0.471	0.445 - 0.497	0.00004
Shooting gallery	973 (27.7)	166 (34.2)	1.36	1.11 - 1.66	0.504	0.475 - 0.532	0.00086
Graveyard, cemetery, burial ground	749 (21.3)	88 (18.1)	0.82	0.64 - 1.04	0.476	0.450 - 0.502	-0.00190
Other place	956 (27.2)	107 (22.0)	0.76	0.60 - 0.95	0.487	0.460 - 0.513	0.00008
Injected with in prior 6 mo.:							
Alone	1735 (49.4)	254 (52.3)	1.12	0.93 - 1.36	0.483	0.456 - 0.511	-0.00048
Spouse/sexual partner	39 (1.1)	13 (2.7)	2.45	1.30 - 4.62	0.468	0.441 - 0.496	0.00018
One other person	1503 (42.8)	203 (41.8)	0.96	0.79 - 1.16	0.474	0.447 - 0.501	-0.00048
Multiple other persons	1272 (36.2)	186 (38.3)	1.09	0.90 - 1.33	0.463	0.435 - 0.490	0.00045
Number of persons injected with in prior 30 days							
None	1049 (29.8)	137 (28.2)	Reference				
1 to 5	1688 (48.0)	249 (51.2)	1.13	0.90 - 1.41	0.481	0.454 - 0.509	-0.00262
6 to 10	429 (12.2)	51 (10.5)	0.91	0.65 - 1.28			
11 or more	297 (8.5)	41 (8.4)	1.06	0.73 - 1.53			
Needle/syringe exchange program use in prior 6 mo.	1464 (41.6)	255 (52.5)	1.55	1.28 - 1.87	0.522	0.494 - 0.550	0.00225
Opioid agonist therapy in past 6 mo.	838 (23.8)	113 (23.3)	0.97	0.77 - 1.21	0.456	0.429 - 0.483	-0.00125
Incarcerated in prior 6 mo.	286 (8.1)	41 (8.4)	1.04	0.74 - 1.46	0.454	0.427 - 0.481	0.00013

Characteristic	Did not recruit undiagnosed PWID (N=3516) n (col %)/ median (IQR)	Recruited undiagnosed PWID (N=486) n (col %)/ median (IQR)	Odds Ratio	95% CI	AUROC	95% CI	VIMP
Network size							
PWID network size† (model by one ln)	15 (6 - 40)	20 (8 - 50)	1.10	1.03 - 1.18	0.534	0.507 - 0.562	-0.00465
PWID network size†							
10 or less	1367 (38.9)	152 (31.3)	Reference				
11 to 20	773 (22.0)	113 (23.3)	1.31	1.01 - 1.70	0.516	0.489 - 0.543	--
21 to 50	812 (23.1)	129 (26.5)	1.43	1.11 - 1.83			
50 or more	564 (16.0)	92 (18.9)	1.47	1.11 - 1.93			

PWID: person who injects drugs; IQR: interquartile range; CI: confidence interval; AUROC: area under the receiver operator curve from univariable logistic model; VIMP: variable importance from random forest; HCV: Hepatitis C virus; ln: natural log

*AUROC not calculable due to small number of observations in some cells; †Number of PWID they personally know in their city; --Characteristic not included in random forest.

Table 4.2 Multivariable models of recruiting an undiagnosed HIV-infected PWID and their predictive accuracy

	Model 1: Logistic predictors only		Model 2: Random forest predictors only		Model 3: Logistic and random forest predictors	
Characteristic	**Adjusted odds ratio**	**95% CI**	**Adjusted odds ratio**	**95% CI**	**Adjusted odds ratio**	**95% CI**
Female (reference=male/*hijra*)	--		1.06	0.23 - 5.02	1.05	0.22 - 4.97
HIV/HCV status						
HIV and HCV negative	Reference		Reference		Reference	
HIV positive/HCV negative	1.32	0.79 - 2.21	1.34	0.80 - 2.24	1.30	0.78 - 2.18
HIV negative/HCV positive	1.24	0.99 - 1.57	1.31	1.04 - 1.65	1.24	0.98 - 1.56
HIV and HCV positive	1.50	1.14 - 1.98	1.59	1.21 - 2.08	1.47	1.11 - 1.94
Sexual partners in prior 6 mo.						
None	Reference				Reference	
1	0.87	0.71 - 1.08	--	--	0.86	0.70 - 1.07
2 or more	0.83	0.62 - 1.13			0.84	0.62 - 1.15
Drugs ever injected						
Heroin only	Reference				Reference	
Buprenorphine/other pharmaceuticals only	1.86	1.08 - 3.21	--	--	1.79	1.03 - 3.12
Combination	1.39	0.80 - 2.41			1.37	0.79 - 2.40
Drugs injected in prior 6 mo.:						
Buprenorphine	1.00	0.77 - 1.30	--	--	1.05	0.80 - 1.38
Stimulants	--		1.55	0.44 - 5.45	1.88	0.53 - 6.70
Sedatives	--		1.02	0.76 - 1.37	1.00	0.74 - 1.34
Place injected in prior 6 mo.:						
Friend's house	--		0.84	0.65 - 1.08	0.89	0.69 - 1.15
Public toilet	--		0.89	0.70 - 1.12	0.91	0.72 - 1.16
Shooting gallery	1.20	0.96 - 1.50	1.18	0.94 - 1.48	1.14	0.90 - 1.44
Other place	--		0.74	0.59 - 0.94	0.75	0.59 - 0.95
Injected with in prior 6 mo.:						
Spouse/sexual partner	--		2.39	1.25 - 4.58	2.44	1.27 - 4.66
Multiple other persons	--		1.12	0.91 - 1.37	1.10	0.89 - 1.35
Needle/syringe exchange program use in prior 6 months	1.26	1.01 - 1.56	1.34	1.08 - 1.65	1.26	1.01 - 1.57
Incarcerated in prior 6 mo.	--		1.06	0.75 - 1.50	1.06	0.75 - 1.51
PWID network size[†] (by increase in one ln)	1.09	1.02 - 1.17	--	--	1.09	1.01 - 1.17
AUROC	0.573	0.546 - 0.600	0.567	0.539 - 0.594	0.575	0.548 - 0.602

PWID: people who inject drugs; CI: confidence interval; HCV: Hepatitis C virus; ln: natural log; AUROC: area under the receiver operator curve

[†]Number of PWID they personally know in their city

Table 4.3 Characteristics by RDS coupon system, recruits of each coupon system, and number of recruitment coupons received

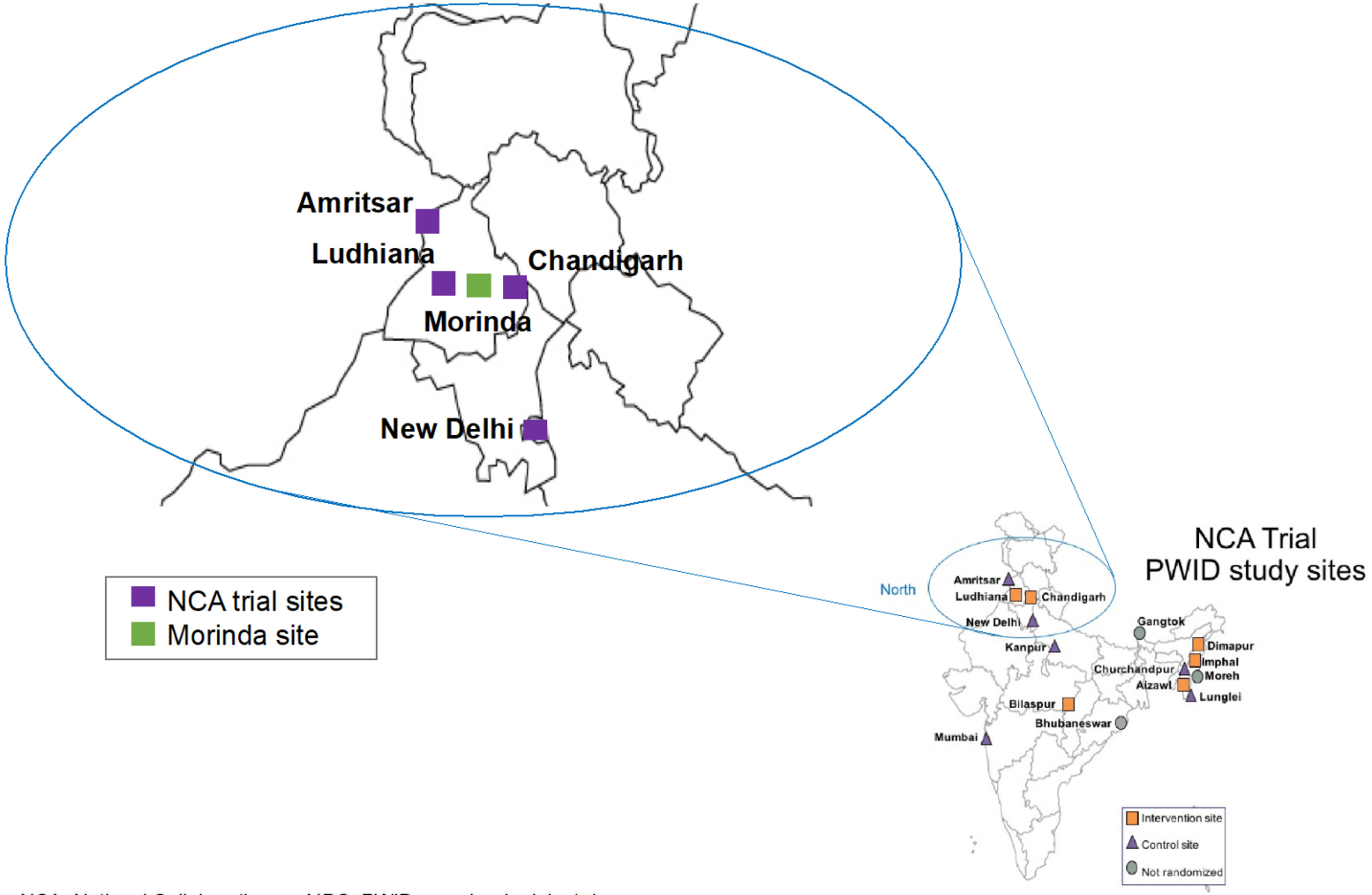
Characteristic n (column %)/ median (IQR)	**Randomized to normal coupon system (N=643)**	**Randomized to altered coupon system (N=646)**	**Recruits of normal coupon system (N=475)**	**Recruits of altered coupon system (N=810)**	**Recruits of altered system who received 2 coupons (N=221)**	**Recruits of altered system who received 5 coupons (N=589)**
Age (years)	27 (22 - 33)	26 (22 - 34)	26 (23 - 33)	27 (22 - 33)	26 (22 - 34)	27 (23 - 33)
Currently married	271 (42.2)	249 (38.5)	188 (39.6)	332 (41.0)	92 (41.6)	240 (40.8)
Education						
No/primary school	103 (16.0)	96 (14.9)	66 (13.9)	133 (16.4)	34 (15.4)	99 (16.8)
Secondary school	377 (58.6)	378 (58.5)	286 (60.2)	466 (57.5)	131 (59.3)	335 (56.9)
At least high school graduate	163 (25.4)	172 (26.6)	123 (25.9)	211 (26.1)	56 (25.3)	155 (26.3)
Tested for HIV in prior year	222 (34.5)	242 (37.5)	179 (37.7)	284 (35.1)	50 (22.6)	234 (39.7)
HIV/HCV status						
HIV and HCV negative	347 (54.0)	349 (54.0)	274 (57.7)	422 (52.1)	126 (57.0)	196 (50.3)
HIV positive/HCV negative	6 (0.9)	10 (1.6)	7 (1.5)	9 (1.1)	0 (0)	9 (1.5)
HIV negative/HCV positive	222 (3.5)	229 (35.5)	157 (33.1)	292 (36.1)	78 (35.3)	214 (36.3)
HIV and HCV positive	68 (10.6)	58 (9.0)	37 (7.8)	8 (10.7)	17 (7.7)	70 (11.9)
Undiagnosed HIV infection (among all)	52 (8.1)	42 (6.5)	29 (6.1)	65 (8.0)	12 (5.4)	53 (9.0)
Undiagnosed HIV infection (among HIV positives)	52 (70.3)	42 (61.8)	29 (65.9)	65 (67.7)	12 (70.6)	53 (67.1)
Undiagnosed HCV infection (among HCV positives)	258 (89.0)	256 (89.2)	173 (89.2)	338 (89.2)	84 (88.4)	254 (89.4)
Injection drug use frequency in prior 6 mo.						
None	131 (20.4)	136 (21.1)	92 (19.4)	175 (21.6)	54 (24.4)	121 (20.5)
Less than daily	370 (57.5)	375 (58.1)	268 (56.4)	474 (58.5)	123 (55.7)	351 (59.6)
Daily	142 (22.1)	135 (20.9)	115 (24.2)	161 (19.9)	44 (19.9)	117 (19.9)
Drugs injected in prior 6 mo. (among active injectors)						
Buprenorphine only	39 (7.6)	50 (9.8)	32 (8.4)	57 (9.0)	13 (7.8)	44 (9.4)
Heroin only	105 (20.5)	107 (21.0)	93 (24.3)	119 (18.7)	34 (20.4)	85 (18.2)
Cocaine only	3 (0.6)	2 (0.4)	1 (0.3)	4 (0.6)	0 (0)	4 (0.9)
Pharmaceuticals only	4 (0.8)	4 (0.8)	2 (0.5)	6 (0.9)	1 (0.6)	5 (1.1)
Combination use	361 (70.5)	347 (68.0)	255 (66.6)	449 (70.7)	119 (71.3)	330 (70.5)
Shared needle/syringe in prior 6 mo. (among active injectors)	134 (26.2)	138 (27.1)	105 (27.4)	166 (26.1)	39 (23.4)	127 (27.1)
Needle/syringe exchange program use in prior 6 mo.	228 (35.5)	216 (33.4)	162 (34.1)	278 (34.3)	62 (28.1)	216 (36.7)

Characteristic n (column %)/ median (IQR)	**Randomized to normal coupon system (N=643)**	**Randomized to altered coupon system (N=646)**	**Recruits of normal coupon system (N=475)**	**Recruits of altered coupon system (N=810)**	**Recruits of altered system who received 2 coupons (N=221)**	**Recruits of altered system who received 5 coupons (N=589)**
Opioid agonist therapy in past 6 mo.	172 (26.8)	194 (30.0)	135 (28.4)	229 (28.3)	45 (20.4)	184 (31.2)
Sexual partners in prior 6 mo.						
None	284 (44.2)	292 (45.2)	225 (47.4)	351 (43.3)	97 (43.9)	254 (43.1)
1	324 (50.4)	317 (49.1)	219 (46.1)	421 (52.0)	114 (51.6)	307 (52.1)
2 or more	35 (5.4)	37 (5.7)	31 (6.5)	38 (4.7)	10 (4.5)	28 (4.8)
Incarcerated in prior 6 mo.	8 (1.2)	17 (2.6)	10 (2.1)	14 (1.7)	2 (0.9)	12 (2.0)
PWID network size[†]						
10 or less	272 (42.3)	270 (41.8)	211 (44.4)	331 (40.9)	85 (38.5)	246 (41.8)
11 to 20	244 (38.0)	249 (38.5)	180 (37.9)	313 (38.6)	92 (41.6)	221 (37.5)
21 to 50	115 (17.9)	115 (17.8)	74 (15.6)	155 (19.1)	42 (19.0)	113 (19.2)
50 or more	12 (1.9)	12 (1.9)	10 (2.1)	11 (1.4)	2 (0.9)	9 (1.5)

RDS: respondent-driven sampling; IQR: interquartile range; HCV: Hepatitis C virus; PWID: people who inject drugs

[†] Number of PWID they personally know in their city

Figure 4.1 Map of North NCA trial PWID sites and Morinda study site, India



NCA: National Collaboration on AIDS; PWID: people who inject drugs

Figure 4.2 Morinda randomization and coupon distribution flow diagram

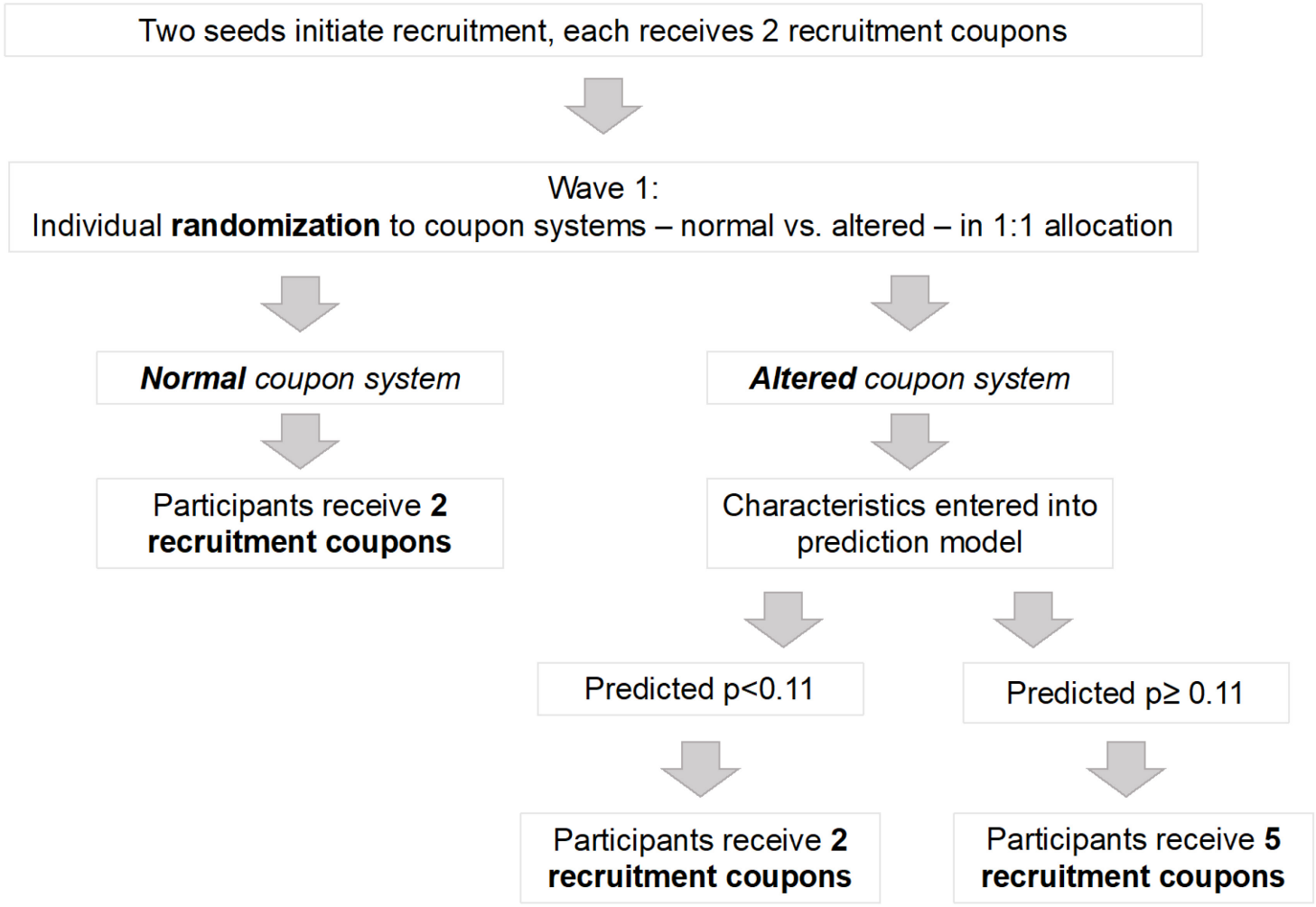


Figure 4.3 Sensitivity and specificity of prediction model probability cut-offs

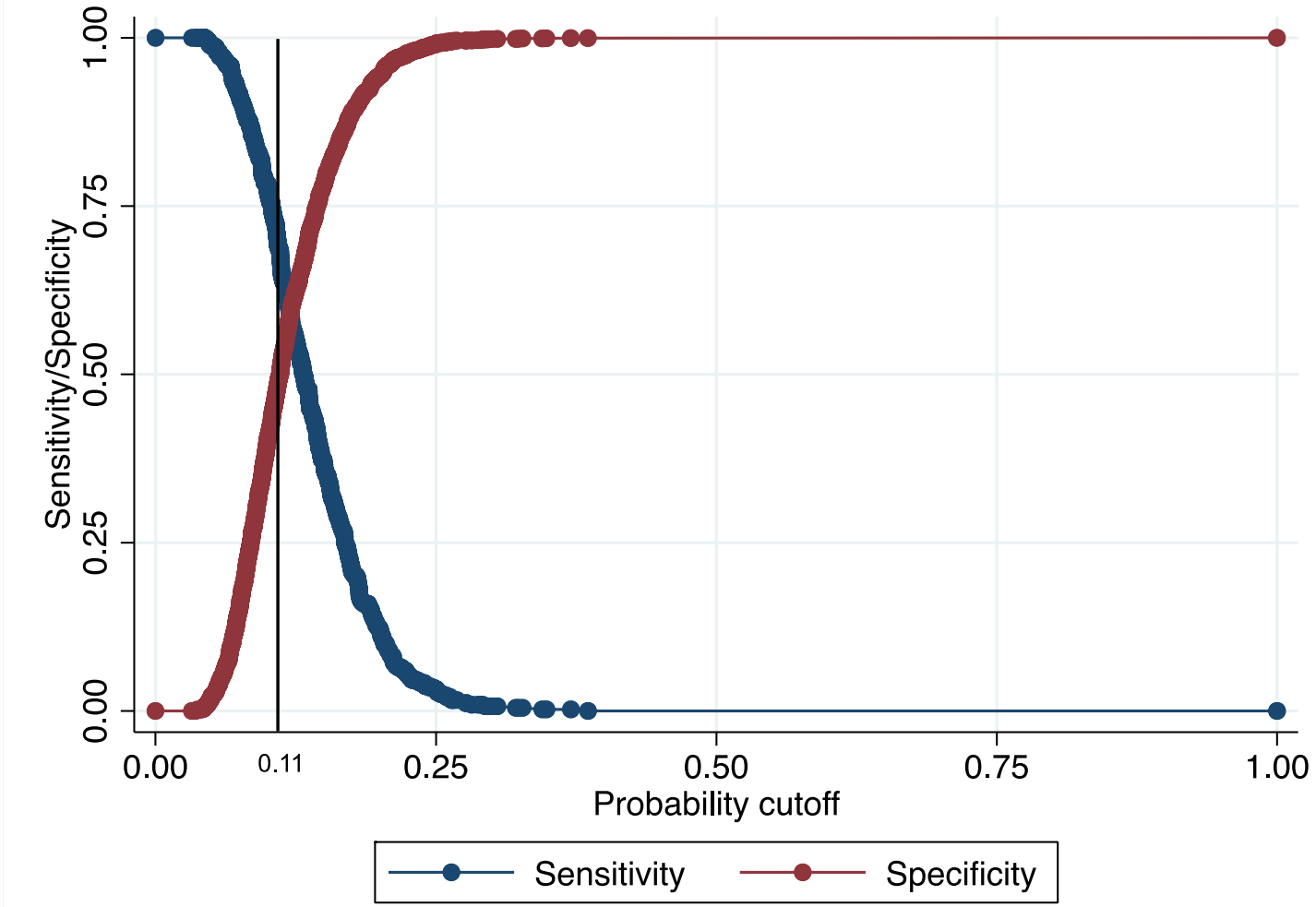
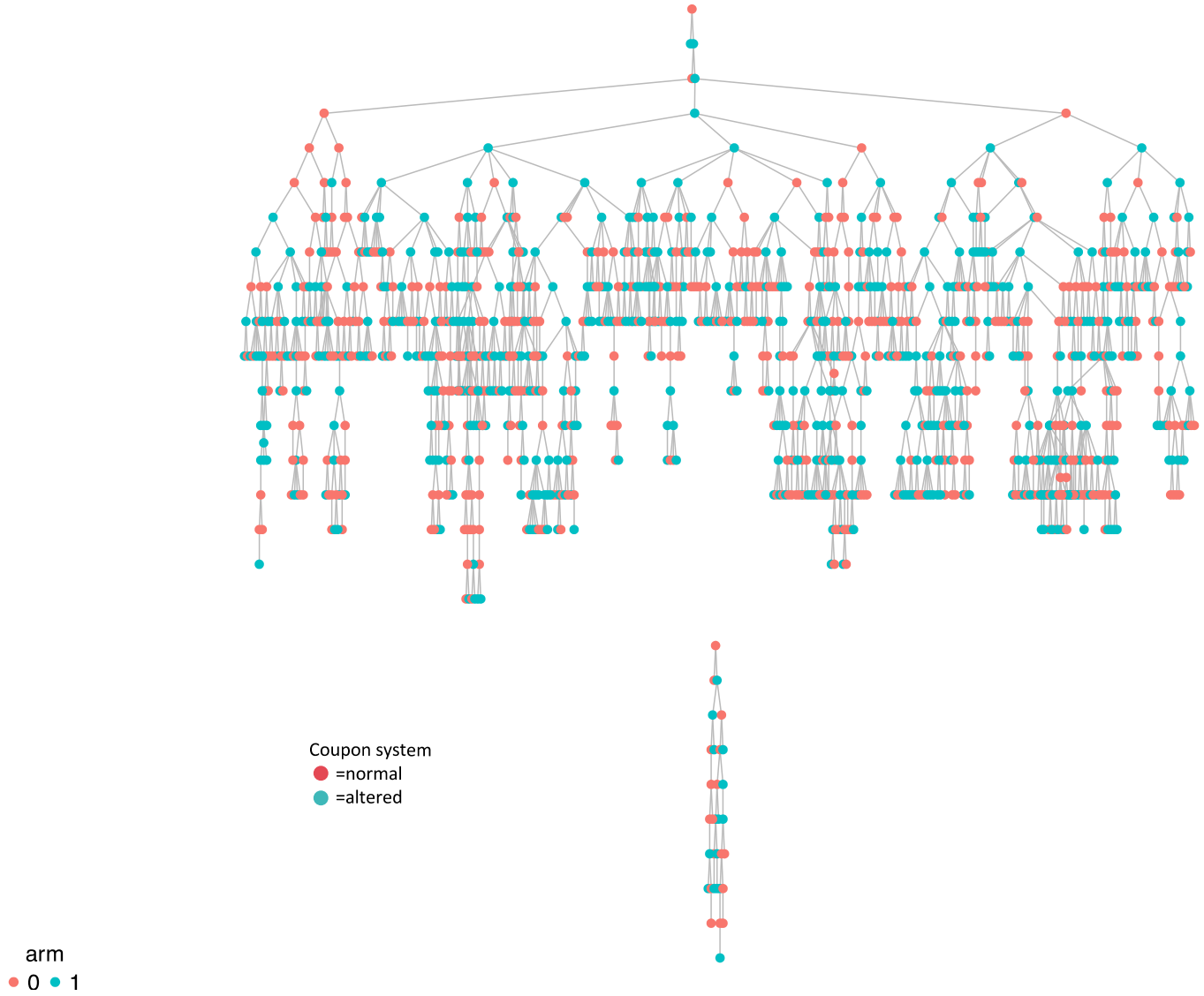


Figure 4.4 RDS recruitment tree of PWID by coupon system, Morinda, India



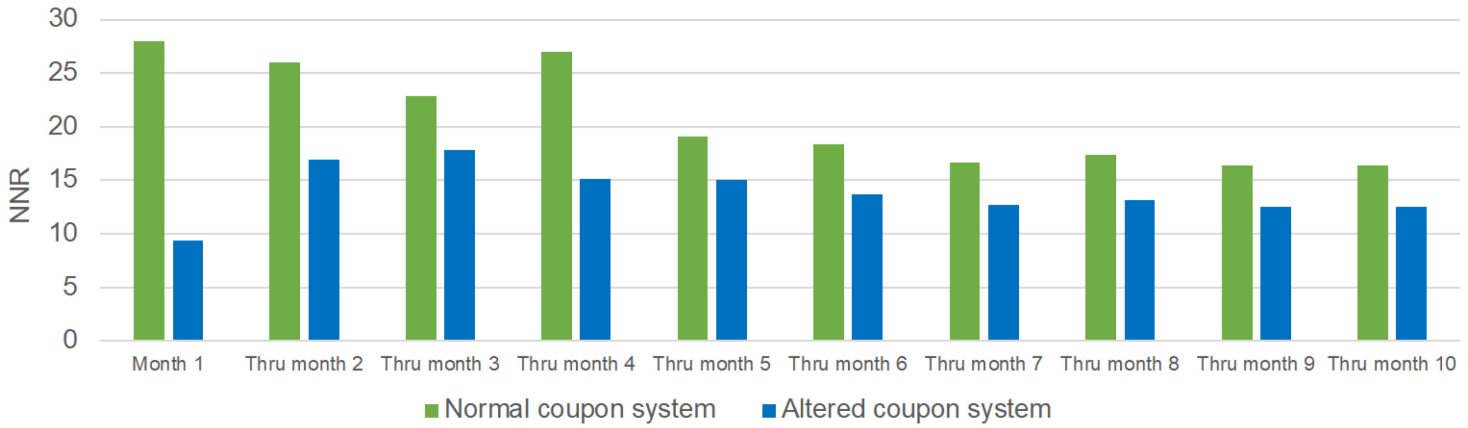
Supplementary Table 4.1 Recruit characteristics by recruiter's RDS coupon system arm, among those with predicted high probability

Characteristic n (column %)/ median (IQR)	**Recruits of normal coupon system with high probability (N=252)**	**Recruits of altered system who received 5 coupons (N=589)**
Age (years)	26 (23 - 33)	27 (23 - 33)
Currently married	94 (37.3)	240 (40.8)
Education		
No/primary school	38 (15.1)	99 (16.8)
Secondary school	157 (62.3)	335 (56.9)
At least high school graduate	57 (22.6)	155 (26.3)
Tested for HIV in prior year	87 (34.5)	234 (39.7)
HIV/HCV status		
HIV and HCV negative	148 (58.7)	196 (50.3)
HIV positive/HCV negative	4 (1.6)	9 (1.5)
HIV negative/HCV positive	75 (29.8)	214 (36.3)
HIV and HCV positive	25 (9.9)	70 (11.9)
Undiagnosed HIV infection (among all)	20 (7.9)	53 (9.0)
Undiagnosed HIV infection (among HIV positives)	20 (69.0)	53 (67.1)
Undiagnosed HCV infection (among HCV positives)	89 (89.0)	254 (89.4)
Injection drug use frequency in prior 6 mo.		
None	50 (19.8)	121 (20.5)
Less than daily	148 (58.7)	351 (59.6)
Daily	54 (21.4)	117 (19.9)
Drugs injected in prior 6 mo. (among active injectors)		
Buprenorphine only	16 (7.9)	44 (9.4)
Heroin only	56 (27.7)	85 (18.2)
Cocaine only	1 (0.5)	4 (0.9)
Pharmaceuticals only	2 (1.0)	5 (1.1)
Combination use	127 (62.9)	330 (70.5)
Shared needle/syringe in prior 6 mo. (among active injectors)	62 (30.7)	127 (27.1)
Needle/syringe exchange program use in prior 6 mo.	84 (33.3)	216 (36.7)
Opioid agonist therapy in past 6 mo.	65 (25.8)	184 (31.2)
Sexual partners in prior 6 mo.		
None	124 (49.2)	254 (43.1)
1	108 (42.9)	307 (52.1)
2 or more	20 (7.9)	28 (4.8)
Incarcerated in prior 6 mo.	6 (2.4)	12 (2.0)
PWID network size[†]		
10 or less	110 (43.7)	246 (41.8)
11 to 20	105 (41.7)	221 (37.5)
21 to 50	33 (13.1)	113 (19.2)
50 or more	4 (1.6)	9 (1.5)

RDS: respondent-driven sampling; IQR: interquartile range; HCV: Hepatitis C virus; PWID: people who inject drugs

[†] Number of PWID they personally know in their city

Supplementary Figure 4.1 NNR over months of recruitment, by recruiter's coupon system



NNR: number needed to recruit undiagnosed HIV-infected people who inject drugs

Chapter 5: Discussion

SUMMARY OF FINDINGS

This work informs the utility and implementation of an intervention strategy using RDS that seeks to improve levels of diagnosis among HIV-infected PWID by first leveraging a large existing RDS data set from diverse regions of India and then, testing a novel RDS coupon system in a city in Punjab, India.

In Chapter 2 (Aim 1), using data from over 14,000 unique persons in six Indian cities, we found RDS required screening fewer PWID and more rapidly identified undiagnosed HIV-infected PWID compared to ICCs (a venue-based strategy). The NNR - interpreted as the average number of PWID recruited/screened in order to find one undiagnosed HIV-infected PWID - for the ICC was 26.1 while for the RDS it was 10.9. Therefore, on average, RDS required screening 15 fewer PWID in order to identify one undiagnosed PWID compared to ICCs. Across all six cities, ICCs identified 2.7 undiagnosed HIV-infected PWID per week while the RDS identified 18.6 per week. Therefore, on average, RDS identified nearly 16 more undiagnosed PWID each week compared to ICCs. Substantial differences in efficiency (i.e., NNR and identification rate) between RDS and ICCs were seen in all six cities individually, with the exception of the NNR in Bilaspur, in which RDS and the ICC results were similar.

After accounting for suppressed HIV viral load among those self-reporting no prior diagnosis in the RDS, differences between the RDS and ICC in terms of efficiency persisted. After restricting to the first 1000 ICC clients to have comparable sample sizes between the RDS and ICC, significant differences in efficiency remained. Other comparative investigations of the ability of

RDS to identify undiagnosed PLWH from injecting and other vulnerable populations found mixed results; some found RDS to identify more while others found other strategies such as venue-based to be more efficient[1-4]. We also found population demographics varied across RDS and ICCs; men, those widowed/divorced/separated, and with higher education were more likely to be RDS participants than ICC clients.

Looking at temporal trends in the NNR and identification rate, both were quite stable over the approximate 2-year time period in the ICCs. The NNR for RDS overall appears to increase over time, though this pattern was not consistent across all cities. The identification rate for RDS overall shows a sharp increase in the beginning and then a slow decrease over time, though, again, this pattern was not consistent across all cities. In Ludhiana, a city in north India, where we were able to map area of residence for PWID, data suggest that RDS reaches PWID that live farther from the RDS study site while ICC clients generally reside closer to the ICC in the central area of the city. The mean distance between an RDS participant's pin code and the RDS site was higher (11.2km) compared to the mean distance for ICC clients (7.5 km) and those that were both ICC clients and RDS participants (9.2 km).

In Chapter 3 (Aim 2), we explored the ability of ten easy-to-collect characteristics of PWID - socio-demographics, injection duration, sharing needles/syringes, NEP and OAT utilization, network size, and HIV and HCV status - to predict which individuals were most likely to know and recruit an undiagnosed/viremic PLWH into an RDS using data from 14,481 PWID RDS participants in 15 different Indian cities. HIV and HCV infection in addition to factors associated with higher HIV risk were most strongly associated with recruiting an undiagnosed and viremic

PLWH. Among PWID with HIV/HCV co-infection, a large network size (≥51), and that reported sharing needles/syringes in the prior six months, a quarter recruited at least one undiagnosed PLWH and a third recruited a viremic PLWH. Other researchers have found a similar recruitment pattern in terms of HIV status; HIV-infected RDS participants are more likely to recruit network members that are also HIV-infected[5,6].

A multivariable model with all ten characteristics was able to predict with moderate ability the recruitment of an undiagnosed (AUROC=0.67) and viremic (0.66) PLWH. A restricted model with only HIV/HCV status and network size was also moderately predictive (undiagnosed AUROC=0.64; viremic AUROC=0.65). When the full model was applied to different contexts across India, it performed best (i.e., higher AUROC) in areas with low harm reduction access. For recruitment of an undiagnosed PLWH, prediction was also higher in settings with low HIV/HCV services availability or accessibility as well as areas with emerging or ongoing epidemics (i.e., high HIV incidence). For recruitment of viremic PLWH, no HIV- or HCV-related community-level characteristics were correlated with predictive ability.

In Chapter 4 (Aim 3), among an RDS sample of 1289 PWID in Morinda, Punjab, an altered RDS coupon system in which individuals more likely to recruit undiagnosed HIV-infected PWID were provided more recruitment coupons did not significantly improve the efficiency of identification of undiagnosed PWID over the normal/traditional coupon system in which all participants receive the same number of coupons, regardless of characteristics. The NNR for the normal coupon system was 16.4 compared to an NNR of 12.5 for the altered system (difference=3.9, 95% CI: -1.6 to 13.1). Characteristics such as HIV and HCV infection, PWID network size,

utilization of needle/syringe exchange programs, and the injection environment - where PWID and with whom they inject - were used to determine which individuals received more recruitment coupons.

Notably, characteristics' predictive ability was generally quite low, suggesting recruitment and/or the network composition of our target population did not have strong enough patterns to steer an RDS to more efficiently identify undiagnosed PWID. However, more coupons distributed throughout the local PWID network from the altered system did result in a higher absolute number of undiagnosed HIV-infected PWID each week compared to the normal system (1.7 vs. 0.8/week). There is scarce prior work on the effect of differential coupon distribution on steering an RDS sample to preferentially identify sub-groups of a population, such as those HIV-infected, undiagnosed, viremic, with high-risk behaviors, etc. Increasing compensation for recruitment of specific types of individuals has seen mixed results[7,8].

PUBLIC HEALTH SIGNIFICANCE AND IMPLICATIONS

Reaching the UNAIDS 90-90-90 target in order to bring an end to the HIV epidemic requires not only implementing evidence-based prevention and care interventions but also scaling these up to reach all people that need them and finding new strategies to make marked progress in the care continuum. Furthermore, addressing disparities among key populations so that they are not left behind is crucial to reach the UNAIDS target and ultimately see HIV incidence dramatically decrease worldwide[9]. Currently, PWID and other key populations, often the hardest to reach and engage, have not benefited to the same extent from improvements in HIV prevention and therapy. They frequently lag behind in the care continuum[10] and are experiencing growing

epidemics across the globe. Outside of sub-Saharan Africa, key populations (including sex workers, MSM, PWID, transgender individuals, and sexual partners of key populations) accounted for 80% of new infections in 2015[11]. Even within sub-Saharan Africa, a quarter of new infections were seen among key populations. Injection drug use is a major driver of HIV globally. PWID account for an estimated 30% of new infections outside of sub-Saharan Africa[12]. In India, PWID consistently experience a higher burden of HIV than the general population and other vulnerable populations (i.e., MSM and female sex workers)[12] with sub-optimal progress along the care continuum, especially at diagnosis[13].

The findings of this dissertation highlight a potentially promising way to close the gap for PWID at diagnosis by utilizing RDS beyond its traditional purpose of gathering data on a representative sample. The higher efficiency of RDS in identifying undiagnosed HIV-infected PWID when compared to the ICCs was striking, despite ICCs being specifically designed to address the needs of PWID in a stigma- and discrimination-free environment and the use of peer outreach workers to visit hot spots to encourage PWID to attend the ICC. This finding underscores the importance and effectiveness of leveraging peer networks to reach and engage PLWH in order to address gaps in the care continuum. Some people will not be aware of the services at a venue-based approach like ICCs because of where/with whom they inject or being on the periphery of a network, for example, or some may be aware of the venue but simply not be motivated to utilize it. Peer connections, peer pressure - in a positive way, and modest monetary compensation, critical parts of RDS, reach and encourage those that do not visit places like ICCs. Specifically, results from this work show RDS reached HIV-infected PWID not actively engaged in HIV testing services provided either at ICCs or targeted interventions by the government of India. It

should be noted, however, that ideally, both approaches would be used to provide HIV prevention, care, and treatment. RDS can quickly identify individuals from the community but those uninfected need continued engagement with prevention services and those infected require lifelong care and treatment, services that a one-time RDS cannot provide.

An in-depth exploration of RDS recruitment patterns showed that there were identifiable predictors of recruiting an undiagnosed HIV-infected PWID into the RDS, one of the strongest being HIV/HCV infection. Those infected with either HIV/HCV or both were more likely to recruit an undiagnosed PWID. While other prior research also found recruitment homophily by HIV-infection status, our findings indicate that PLWH may be connected to *undiagnosed* PLWH, a pattern that could be leveraged to reach undiagnosed persons. Additionally, the association with recruiter HCV infection is, to our knowledge, a new finding. Though HCV is seen in the general population, the burden is especially high among PWID, with more than 50% infected[14]. For individuals, HCV is a strong indicator of current or past high-risk injection behaviors or characteristics in addition to a predictor of being connected to others with high-risk behaviors or characteristics, thus those likely to be HIV-infected and undiagnosed.

When the full prediction model of recruiting an undiagnosed HIV-infected PWID in Aim 2 was applied to different settings in India, results suggest that utilizing an RDS-based approach using HIV/HCV status and basic, easy-to-collect characteristics to identify more undiagnosed HIV-infected PWID may be most appropriate for communities with growing HIV epidemics and low PWID-targeted harm reduction and HIV/HCV service utilization. If there is little prior information on the local epidemic and service utilization, an abbreviated RDS could be

conducted for at least 5-6 waves to characterize the epidemic and population in order to determine appropriateness of the predictive model for that particular setting. Additionally, results imply the model may not be easily applied for the purposes of identifying viremic PLWH, given the different compositions of viremic populations (i.e., undiagnosed, diagnosed but not linked to care/ART, and sub-optimal adherence to ART) in different communities. It is important to note that the predictive abilities of individual characteristics as well as the full model were lower than hypothesized.

With detailed information on who recruits undiagnosed HIV-infected PWID into an RDS, the next important question is how to *use* this information to identify undiagnosed PWID more efficiently. There is very little prior research on steering an RDS to preferentially recruit a particular sub-group in a population and, to our knowledge, none that specifically use a data-driven approach by first identifying patterns in RDS recruitment. In Morinda, we formally tested whether provision of more recruitment coupons to those more likely to recruit an undiagnosed HIV-infected PWID results in finding more undiagnosed PWID, using predictors identified from existing RDS data in the same region of India. The efficiency, measured in terms of the NNR, between the two systems was not significantly different, suggesting that in this setting, a typical RDS in which all individual receive the same number of coupons works just as well as a targeted system in identifying undiagnosed HIV-infected PWID. However, the absolute number of undiagnosed PWID identified by the altered system was more than twice the number identified by the normal system as a consequence of more than twice the number of PWID recruited in total via the altered system. In an urgent situation such as an outbreak, reaching as many individuals as possible as quickly as possible with HIV testing and counseling is critical. Our

results suggest that increasing the number of coupons could make the overall recruitment process more rapid with more undiagnosed HIV-infected PWID identified quickly.

LIMITATIONS AND STRENGTHS

There are several limitations to this work that should be noted. Diagnosis status among those HIV-infected was self-reported in all analyses using data collected via an interviewer-administered questionnaire. Well-trained interviewers are used to mitigate recall or reporting bias but are unable to eliminate it entirely. Validating the diagnosis status for all those HIV-infected by checking records at local testing centers would be extremely resource and time intensive and require collecting personal identifiers from all participants. For RDS data collected in the NCA trial, viral load was available for all HIV-infected participants so it was possible to re-categorize those not self-reporting a prior diagnosis but with a suppressed viral load as diagnosed. Sensitivity analyses in Aim 1 after this re-categorization did not change overall inferences. However, corrections for any other scenario is not possible, such as reporting a prior diagnosis when they were truly not or not reporting a prior diagnosis when they truly were but were viremic. Correction using viral load was not possible for ICC clients since viral load is not standard of care and was not routinely collected from clients.

Cities selected for the NCA trial were not a random selection of cities in India; rather cities were selected in discussion with NACO, India to represent different HIV and injection drug use epidemics and were generally large, metropolitan cities[15]. Therefore, findings may not reflect PWID in other regions or more rural areas of India not represented in the NCA trial. Relatedly, findings may not be transportable to other regions of the world, where PWID network dynamics,

HIV prevention services, and care continuum outcomes differ from what is observed in India. The altered RDS coupon system was tested in only one community. The effectiveness of this approach in identifying undiagnosed HIV-infected PWID should not be concluded by just one study in one location. Additionally, the true difference in NNR between the two coupon systems may be meaningful but small, requiring a larger sample size than was collected in Morinda.

There are also several strengths to this body of work. First, the large amount of RDS data from diverse Indian settings collected as part of the NCA trial allowed for an in-depth exploration of recruitment patterns. More than 14,000 PWID were recruited for the baseline assessment of the trial, which is, to our knowledge, one of the largest samples collected using RDS, especially in an LMIC setting. Additionally, detailed socio-demographic, network, and risk behaviors and characteristics were collected via the study questionnaire and provided an opportunity for a thorough investigation of potential predictors of recruiting an undiagnosed HIV-infected PWID. Available data from RDS as well as the ICCs from the six intervention cities in the trial also permitted a within-city comparison of RDS and ICCs while identifying overlap between the two using biometric technology, removing any confounding by different population characteristics, environment, and service availability.

While the findings should not be generalized to other settings or populations, the methods used to identify predictors of recruitment within an RDS (i.e., linking recruiters and their recruits then using logistic models and/or random forests to identify predictors) could easily be applied to other key populations in other regions of the world for which RDS is also a common method to recruit study participants (e.g., MSM, sex workers, transgender individuals) for HIV surveillance

and research purposes. The methods could also be extended to other outcomes, such as specific risk behaviors and other HIV care continuum outcomes - for example, recruitment of PWID that report sharing needles/syringes or HIV-infected PWID diagnosed but not currently on treatment.

FUTURE DIRECTIONS

Looking to future work, more research is needed to understand the benefit of RDS over venue-based and other approaches, such as drop-in centers and peer outreach, in other key populations such as MSM and in additional settings outside India with different HIV epidemics. As mentioned earlier, venues such as ICCs or drop-in centers play an important role and should be utilized to the extent that they benefit their target population. Investigating a novel strategy that incorporates RDS into a venue-based approach would be an important line of research, optimizing the benefits of both approaches simultaneously. For example, an RDS with onsite HIV counseling and testing could be run out of a care center (or very close nearby), so that individuals could be linked to appropriate services immediately (i.e., same day), either risk reduction counseling and harm reduction for those HIV-uninfected or care and treatment services for those infected. This type of dual strategy could improve the overall reach and lead to a community-level decrease in risk behaviors and increase in utilization of HIV prevention, care, and treatment services, closing or narrowing the gaps in the care continuum.

More research into RDS recruitment patterns among PWID is also warranted. It is unknown whether similar predictors of recruiting an undiagnosed HIV-infected PWID would be seen in populations in different settings such as high-resource settings (e.g., United States or Europe) or in areas with a generalized HIV epidemic (e.g., sub-Saharan Africa). Consistency across

different settings would allow for widespread utilization of the patterns and findings. It is reasonable to hypothesize that HIV and HCV infection would be strong predictors in other injecting populations but factors such harm reduction utilization and where and with whom they inject may not predict recruitment patterns in other areas. With the large amount of RDS data already collected from PWID and other key populations around the world for HIV surveillance and research, it would be fairly easy to use the existing data to explore recruitment patterns.

Since the altered RDS coupon approach was tested in only one location, replicating this design or a similar design in multiple other settings would strengthen the evidence base for steering an RDS to identify more undiagnosed PWID using differential coupon distribution and guide the implementation of the approach. Since HIV/HCV infection independently were strong predictors, a simplified version of our targeted coupon approach using only HIV and HCV infection from onsite rapid tests would be a very interesting line of future research. In general, there is very little prior work on the effects of differential coupon distribution for enriching a sample with a specific sub-group, therefore, more research in this area is needed. Other RDS alteration strategies besides differential coupon distribution should also be explored further. More research on promising strategies, such as rapid sequential RDS[16] or terminating recruitment chains after a specific number of waves if an individual in the sub-group of interest is not identified[2], would move the field of RDS as an intervention strategy forward.

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of integrated care centers to improve HIV outcomes among men who have sex with men and persons who inject drugs in India. *BMC Health Services Research.* 2016;16(1):652.

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Curriculum Vitae

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Education

Ph.D. candidate	current	Johns Hopkins Bloomberg School of Public Health, General Epidemiology
M.H.S.	2012	Johns Hopkins Bloomberg School of Public Health, General Epidemiology
B.A.	2005	Florida State University, International Affairs and Political Science

Professional Experience

May 2013-current — Sr. Research Data Manger and Analyst, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

Data analyst primarily responsible for statistical analysis of data for several studies in India among people who inject drugs and men who have sex with men investigating HIV prevention/care/treatment and Hepatitis C/liver disease natural history and treatment outcomes. Manage study databases prospectively, conduct quality control, and provide updates on study enrollment and follow-up. Conducted covariate restricted randomization for cluster-randomized trial. Analyses conducted include longitudinal data analysis, trial outcome analyses for individual- and cluster-randomized trial designs, and weighted analyses for respondent-driven sampling (RDS) data. Draft and contribute to scientific conference presentations and peer-reviewed manuscripts. Develop study questionnaires and protocols; train in-country staff on study procedures.

June 2017-February 2018 — HIV/AIDS Implementation Science Data Research Intern, Research Division, Office of HIV/AIDS, USAID

Provide technical support for the Implementation Science Branch with a focus on research and evaluations to improve PEPFAR's HIV/AIDs prevention, care and support, and treatment programs. Main responsibility is the design and implementation of an assessment of the impact of USAID/PEPFAR HIV implementation science investment on HIV prevention, care, and treatment policy and guidance at the program, national, and international levels. Conducted in-depth literature review on research utilization assessment models/frameworks, designed semi-structured questionnaire on research utilization for study investigators, and abstracted data on research utilization from public and USAID-housed documents on implementation science studies funded under the IS APS cooperative agreement. Synthesize data collected via document review and survey and draft methods and results for peer-reviewed manuscript.

September 2012-May 2013 Sr. Research Program Coordinator II, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

Member of research team implementing an evaluation of a community cluster randomized HIV prevention trial to be launched in Iringa, Tanzania. Created research plan and prepared all other documents for submission to the Institutional Review Board. Assisted with development of survey instrument; reviewed and revised survey to ensure correct logic, assess timing, and standardize questions and responses; coordinated translation of instrument from English to Kiswahili. Compiled and drafted sections of detailed research study protocol. Collaborated with co-authors on the scope, protocol, and writing of a paper on sex worker community empowerment strategies. Updated a systematic review on the effectiveness of the empowerment strategies for prevention of HIV/STIs, including database searching, title and abstract reviews, and data abstraction for meta-analysis. Conducted comprehensive search of the peer-reviewed and grey literature as well as practice-based evidence on community empowerment strategies for sex workers.

June 2011-August 2012 Graduate Student Research Assistant, StatEpi Group, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

Analyst supporting epidemiological research related to HIV/AIDS. Collaborated with co-authors in planning and conduction of analyses and presentation of research findings. Performed complex data management such as variable creation and manipulation, data merging, and data cleaning. Conducted statistical analyses including exploratory data analysis and regression modeling such as logistic, Poisson, and survival analysis. Created tables and figures to visualize data and research findings. Wrote and reviewed manuscripts and abstracts for publication and scientific conferences. Reviewed abstracts for inclusion in a systematic review on age-related co-morbidities in HIV-infected patients.

January 2009-August 2010 Senior Program Assistant, Board on Health Care Services, The Institute of Medicine (IOM)

Supported IOM committees with the Board on Health Care Services including the fast-track study on Comparative Effectiveness Research. Prepared contracts with outside vendors and monitored deliverables. Assisted with drafting sections of report and background papers; created and edited figures and tables for committee reports. Organized review comments during external review process. Verified references and performed fact checking for committee reports. Tracked budget throughout the project and compiled quarterly progress reports for client. Planned committee meetings, including coordination of travel, lodging, catering, and briefing materials. Created and managed the Current Project System and Committee Website.

May 2005-June 2008 Program Associate and Intern Coordinator, Professional Exchanges Division, Meridian International Center

Administered the International Visitor Leadership Program on behalf of the U.S. Department of State. Prepared budget and ensured program funds were managed and disbursed according to the client's regulations. Arranged program logistics, including domestic flights, ground

transportation, catering and accommodations. Prepared visitors' biographic information and a detailed schedule of the visitors' arranged meetings. Solved problems efficiently with cultural sensitivity. Recruited, interviewed and selected prospective internship candidates for Professional Exchanges Division. Developed full-time summer internship program and supervised interns.

Teaching Experience

February 2017-current	280.350 Fundamentals of Epidemiology (undergraduate) Discussion Section Instructor

Independently lead discussion (lab) sessions for undergraduate course on basic epidemiology principles, hold office hours, and draft homework/exam questions.

March-May 2017	340.715 Design of Epi Studies: Proposal Development and Critique Teaching Assistant (TA), JHSPH Department of Epidemiology

Coordinate course logistics including faculty review of student proposals, present lecture on peer review and critique for doctoral course on developing proposals for epidemiologic studies.

October-December 2016	340.752 Epidemiologic Methods 2 Teaching Assistant (TA), JHSPH Department of Epidemiology

Co-led lab sessions, held office hours, and piloted exam for graduate-level methods course in epidemiology.

Invited Seminars/Lectures

Identifying undiagnosed HIV-infected people who inject drugs in India using respondent-driven sampling. September 17, 2018. Expert consultation on advancing methods for bio-behavioral surveys (BBS), Centers for Disease Control and Prevention.

Epidemiology of HIV among people who inject drugs and men who have sex with men in India. April 30, 2018. Fundamentals of Epidemiology course (undergraduate).

Respondent-driven Sampling (RDS): Analytical Considerations, October 27, 2017. Tennessee Department of Health-Vanderbilt University Center for AIDS Research.

Honors and Awards

2018	The R. Bradley Sack Family Scholarship Award. To support outstanding JHSPH doctoral students studying infectious disease programs in the developing world.
2018	New Investigator Scholarship. To support travel to and attendance at the Conference on Retroviruses and Opportunistic Infections (CROI) 2018.
2017	Doctoral Thesis Research Fund Award to support doctoral thesis research, Department of Epidemiology

2017	Young Investigator Scholarship. To support travel to and attendance at the Conference on Retroviruses and Opportunistic Infections (CROI) 2017.
2016	Global Health Field Research Award. To support student-initiated research projects in Global Health
2015-2017	Johns Hopkins HIV Epidemiology and Prevention Sciences Training Program (T32) Institutional Training Grant. Pre-doctoral Trainee with full tuition and stipend awarded
2012	Trudy Bush Award, Department of Epidemiology. For research specialization in women's health and scholastic accomplishments.
2011	Merit-based 75% tuition scholarship, Dept. Epidemiology, Johns Hopkins University, 2011-2012
2009	Group Distinguished Service Award, The Institute of Medicine. For outstanding contributions to the work of the National Academies.
2003	Phi Beta Kappa Honor Society. Based on academic achievement in pursuit of a liberal arts education.
2001	Phi Eta Sigma Honor Society. Based on academic achievement during freshman year of undergraduate program.

Peer Reviewer: *Journal of Acquired Immune Deficiency Syndromes*, *Journal of the International AIDS Society*, *PLOS ONE*, *International Journal of STD and AIDS*, *Drug and Alcohol Dependence*, *AIDS Care, Substance Abuse Treatment, Prevention, and Policy,* and Society for Epidemiologic Research annual meeting.

Grants

NIH/NIDA Fellowship (F31) to support doctoral dissertation research; *PI:* **Allison M. McFall**. *Project Title:* Investigating the Potential of Respondent-Driven Sampling to Reach Undiagnosed, Out-of-Care HIV-infected People Who Inject Drugs (DA044046-01A1). *Award period:* September 1, 2017 - March 31, 2019

Journal Articles

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Subbaraman R, Thomas BE, Sellappan S, Suresh C, Jayabal L, Lincy S, Raja AL, **McFall AM**, Solomon SS, Mayer KH, Swaminathan S. Tuberculosis patients in an Indian mega-city: Where do they live and where are they diagnosed? *PLoS One*. 2017 Aug 15;12(8):e0183240.

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McFall AM, Solomon SS, Lucas GM, Celentano DD, Srikrishnan AK, Kumar MS, Mehta SH. Epidemiology of HIV and hepatitis C infection among women who inject drugs in Northeast India: A respondent-driven sampling study. *Addiction*. March 2017.

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Kerrigan D, Kennedy CE, Morgan-Thomas R, Reza-Paul S, Mwangi P, Win KT, **McFall AM**, Fonner VA, Butler J. A community empowerment approach to the HIV response in sex workers: effectiveness, challenges, and considerations for implementation and scale-up. *Lancet,* 2015; 385(9963):172-85.

McFall AM, Dowdy D, Zelaya C, Murphy K, Wilson TE, Young MA, Gandhi M, Cohen MH, Golub ET, Althoff KN. Understanding the Disparity: Predictors of virologic failure in women using highly active antiretroviral therapy vary by race and/or ethnicity. *J Acquir Immune Defic Syndr*, 2013, 64:3.

Book Chapters

Kerrigan D, Kennedy CE, Morgan-Thomas R, Reza-Paul S, Mwangi P, Win KT, **McFall AM**, Fonner VA, Mantsios A, Butler J. Female, Male and Transgender Sex Workers, Epidemiology of HIV/AIDS. In *Encyclopedia of AIDS*. Hope TJ, Stevenson M, Richman D (Ed.). New York, New York: Springer, 2016.

Scientific Conference Presentations

McFall AM, Solomon SS, Srikrishnan AK, Anand S, Vasudevan CK, Lucas GM, Mehta SH. Respondent-driven sampling more efficiently identifies undiagnosed HIV-infected people who inject drugs (PWID) than PWID-targeted community integrated care centers in India. 22nd International AIDS Conference, July 23-27, 2018, Amsterdam, the Netherlands. *(Oral Presentation)*

McFall AM, Mehta SH, Srikrishnan AK, Anand S, Vasudevan CK, Lucas GM, Solomon SS. Identifying undiagnosed HIV-infected PWID in India using respondent-driven sampling. Conference on Retroviruses and Opportunistic Infections (CROI) 2018, Boston, MA, March 4-7, 2018. *(Poster Presentation)*

Boon D, Solomon SS, Srikrishnan AK, **McFall AM**, Balakrishnan P, Iqbal SH, Lucas GM, Laeyendecker O, Quinn TC, Mehta SH. Estimating HIV and HCV incidence among persons who inject drugs in India. Conference on Retroviruses and Opportunistic Infections (CROI) 2018, Boston, MA, March 4-7, 2018. *(Poster Presentation)*

Solomon SS, Solomon S, **McFall AM**, Srikrishnan AK, Anand S, Balakrishnan P, Ogburn E, Moulton L, Kumar MS, Celentano DD, Lucas GM, Mehta SH. Impact of Service Integration on

HIV testing uptake among key populations in India. Conference on Retroviruses and Opportunistic Infections (CROI) 2018, Boston, MA, March 4-7, 2018. *(Poster Presentation)*

McFall, AM, Tomori C, Srikrishnan AK, Solomon SS, Anand S, Vasudevan CK, Mehta SH, Celentano DD. Is there synergy in syndemics? Psychosocial conditions and syphilis among men who have sex with men in India. Society for Epidemiologic Research (SER) 2017, Seattle, Washington, June 20-23, 2017. *(Poster Presentation)*

Solomon SS, **McFall AM**, Lucas GM, Srikrishnan AK, Celentano DD, Kumar MS, Anand S, Wong J, Solomon S, Mehta SH. Finding the hard to reach HIV-infected: respondent-driven sampling as a public health intervention for PWID and MSM. 9th IAS Conference on HIV Science (IAS 2017), Paris France, July 23-26, 2017 *(Poster Presentation)*

McFall AM, Solomon SS, Lucas GM, Srikrishnan AK, Kumar MS, Anand S, Vasudevan CK, Celentano DD, Mehta SH. High HIV incidence among PWID and MSM attending integrated care centers in India. Conference on Retroviruses and Opportunistic Infections (CROI) 2017, Seattle, WA, February 13-16, 2017. *(Poster Presentation)*

Patel EU, Solomon SS, **McFall AM**, Srikrishnan AK, Pradeep A, Yi J, Laeyendecker O, Thomas DL, Sulkowski MS, Mehta SH. Treatment readiness for hepatitis C virus infection among PWID in Chennai, India. Conference on Retroviruses and Opportunistic Infections (CROI) 2017, Seattle, WA, February 13-16, 2017. *(Poster Presentation)*

Solomon SS, Pradeep A, Sulkowski MS, **McFall AM**, Srikrishnan AK, Nandagopal P, Saravanan S, Anand S, Kumar MS, Thomas DL, Mehta SH. Field-based delivery of HCV therapy with minimal monitoring for PWID in Chennai, India. Conference on Retroviruses and Opportunistic Infections (CROI) 2017, Seattle, WA, February 13-16, 2017. *(Poster Presentation)*

Solomon SS, Srikrishnan AK, Anand S, **McFall AM**, Balakrishnan P, Celentano DD, Kumar MS, Lucas GM, Mehta SH. Respondent-driven sampling: An epidemiological tool with interventional potential. Conference on Retroviruses and Opportunistic Infections (CROI) 2016, Boston, MA, February 22-25, 2016. *(Poster Presentation)*

Solomon SS, Lucas GM, Srikrishnan AK, **McFall AM**, Celentano DD, Saravanan S, Kumar MS, Mehta SH. Barriers to viral suppression among key populations in India: The final 90. Conference on Retroviruses and Opportunistic Infections (CROI) 2016, Boston, MA, February 22-25, 2016. *(Poster Presentation)*

Lucas GM, Atta MG, Zook K, **McFall AM**, Mehta SH, Fine DM, Stein JH, Schwartz GJ. Traditional and viral factors associated with iohexol-based GFR slope over 3 years. Conference on Retroviruses and Opportunistic Infections (CROI) 2016, Boston, MA, February 22-25, 2016. *(Poster Presentation)*

Sabri B, Srikrishnan AK, Solomon SS, **McFall AM**, Vasudevan CK, Anand S, Celentano DD, Mehta SH, Kumar MS, Lucas GM. Gender-specific factors related to HIV risks among people

who inject drugs in India. Conference on Retroviruses and Opportunistic Infections (CROI) 2016, Boston, MA, February 22-25, 2016. *(Poster Presentation)*

Solomon SS, **McFall AM**, Srikrishnan AK, Lucas GM, Vasudevan CK, Celentano DD, Kumar MS, Solomon S, Mehta SH. Linkage to HIV care among men who have sex with men and drug users in India: Getting to 90. Conference on Retroviruses and Opportunistic Infections (CROI) 2015, Seattle, WA, February 23-26, 2015. *(Poster Presentation)*

Mehta SH, Solomon S, **McFall AM**, Srikrishnan AK, Balakrishnan P, Nandagopal P, Thomas DL, Sulkowski MS, Solomon SS**.** Rapid progression to cirrhosis and death Among HCV-infected persons who inject drugs in India. Conference on Retroviruses and Opportunistic Infections (CROI) 2015, Seattle, WA, February 23-26, 2015. *(Poster Presentation)*

McFall AM, Solomon SS, Lucas GM, Srikrishnan AK, Kumar MS, Solomon S, Mehta SH. Out of sight, out of mind: High HIV prevalence and low utilization of HIV prevention services among female injection drug users in Northeastern India. 2014 CFAR HIV Research in Women Symposium, December 8-9, 2014, New Rochelle, NY. *(Oral Presentation)*

Solomon SS, Lucas GM, Srikrishnan AK, **McFall AM**, Saravanan S, Laeyendecker O, Kumar MS, Celentano DD, Solomon S, Mehta SH. Monitoring effectiveness of HIV programs in the era of implementation science utilizing a sample of 27,000 drug users and men who have sex with men in India. Controlling the HIV Epidemic with Antiretrovirals: Avoiding the Cost of Inaction by IAPAC, September 18-19, 2014, London, England. *(Oral Presentation)*

Solomon SS, Lucas GM, Srikrishnan AK, **McFall AM**, Saravanan S, Balakrishnan P, Kumar MS, Solomon S, Celentano DD, Mehta SH. High population ART coverage and viral suppression are associated with reduced HIV incidence among MSM and PWID in India. 20th International AIDS Conference, July 20-25, 2014, Melbourne, Australia. *(Poster Presentation)*

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